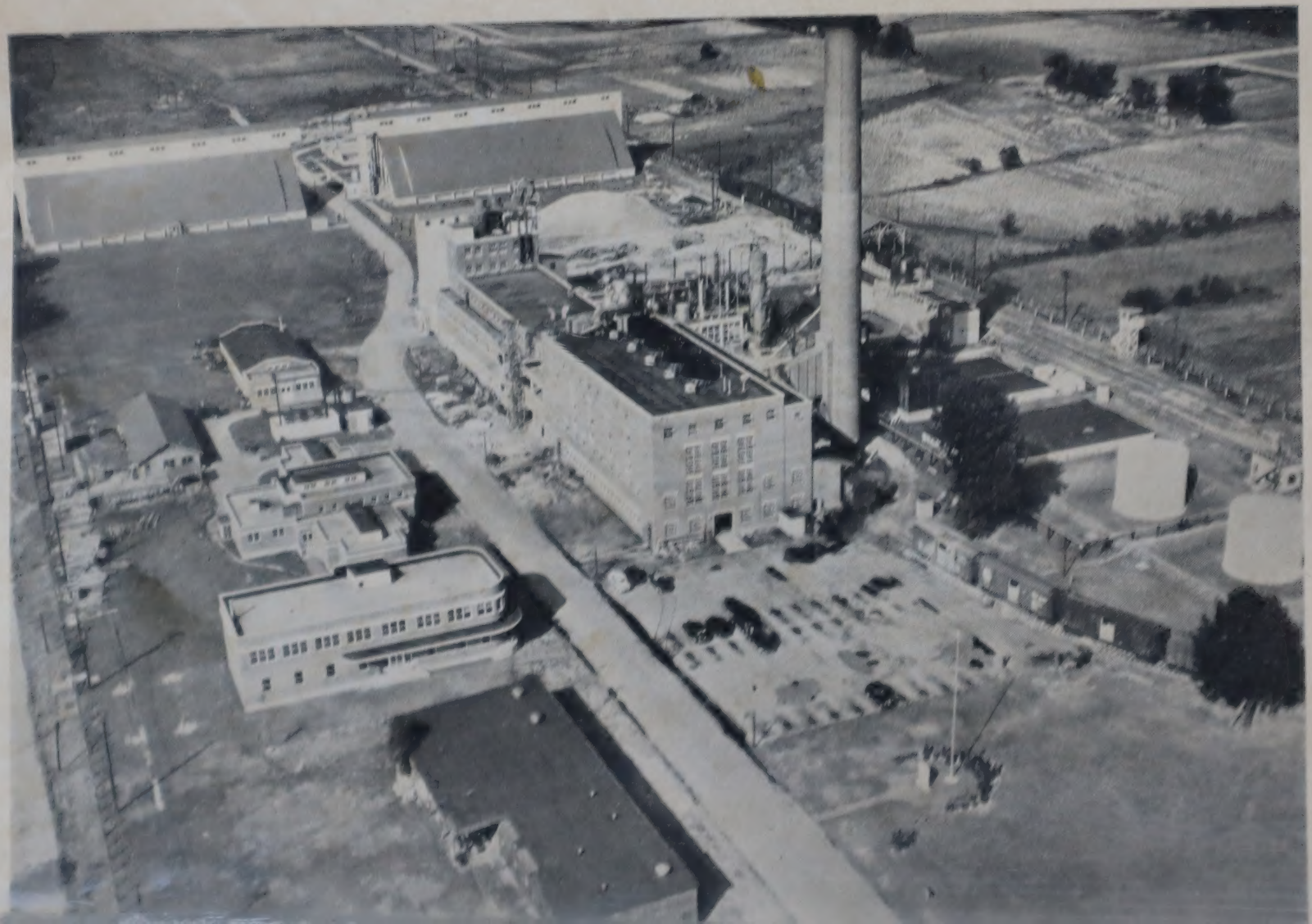
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Furans



THE FURANS

by

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and

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GENERAL INTRODUCTION

American Chemical Society's Series of Chemical Monographs

By arrangement with the Interallied Conference of Pure and Applied Chemistry, which met in London and Brussels in July, 1919, the American Chemical Society was to undertake the production and publication of Scientific and Technologic Monographs on chemical subjects. At the same time it was agreed that the National Research Council, in cooperation with the American Chemical Society and the American Physical Society, should undertake the production and publication of Critical Tables of Chemical and Physical Constants. The American Chemical Society and the National Research Council mutually agreed to care for these two fields of chemical progress. The American Chemical Society named as Trustees, to make the necessary arrangements of the publication of the Monographs, Charles L. Parsons, secretary of the Society, Washington, D. C.; the late John E. Teeple, then treasurer of the Society, New York; and the late Professor Gellert Alleman of Swarthmore College. The Trustees arranged for the publication of the ACS Series of (a) Scientific and (b) Technological Monographs by the Chemical Catalog Company, Inc. (Reinhold Publishing Corporation, successor) of New York.

The Council of the American Chemical Society, acting through its Committee on National Policy, appointed editors (the present list of whom appears at the close of this sketch) to select authors of competent authority in their respective fields and to consider critically the manuscripts submitted.

The first Monograph of the Series appeared in 1921. After twenty-three years of experience certain modifications of general policy were indicated. In the beginning there still remained from the preceding five decades a distinct though arbitrary differentiation between so-called "pure science" publications and technologic or applied science literature. By 1944 this differentiation was fast becoming nebulous. Research in private enterprise had grown apace and not a little of it was pursued on the frontiers of knowledge. Furthermore, most workers in the sciences were coming to see the artificiality of the separation. The methods of both groups of workers are the same. They employ the same instrumentalities, and frankly recognize that their objectives are common, namely, the search for new knowledge for the service of man. The officers of the Society therefore combined the two editorial Boards in a single Board of twelve representative members.

Also in the beginning of the Series, it seemed expedient to construe

rather broadly the definition of a Monograph. Needs of workers had to be recognized. Consequently among the first hundred Monographs appeared works in the form of treatises covering in some instances rather broad areas. Because such necessary works do not now want for publishers, it is considered advisable to hew more strictly to the line of the Monograph character, which means more complete and critical treatment of relatively restricted areas, and, where a broader field needs coverage, to subdivide it into logical subareas. The prodigious expansion of new knowledge makes such a change desirable.

These Monographs are intended to serve two principal purposes: first, to make available to chemists a thorough treatment of a selected area in form usable by persons working in more or less unrelated fields to the end that they may correlate their own work with a larger area of physical science discipline; second, to stimulate further research in the specific field treated. To implement this purpose the authors of Monographs are expected to give extended references to the literature. Where the literature is of such volume that a complete bibliography is impracticable, the authors are expected to append a list of references critically selected on the basis of their relative importance and significance.

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FOREWORD

The publication of this book on Furans is another milestone on the road of progress of oat hulls to furfural and its derivatives, and it supplies a need of long standing in the literature on these materials.

We think it is fair to say that furfural and its derivatives have evolved in a little over thirty years into a new chemical industry, and we, who in 1920 began the oat hull research that resulted in commercial furfural, can only be amazed at its present magnitude and overawed by its promise.

In retrospect, those early days, when we were groping for new or better uses for oat hulls, did not appear to offer either glamour or rich reward, but rather a grim month-by-month challenge on what could best be done to justify the research project.

The evolution of chemical attack was (1) analysis of our raw material, (2) acid hydrolysis to give xylose, (3) study of xylose and (4) furfural—mere traces at first, then visible quantities and, finally, furfural in drums and tank cars. We believe the first glimmer of hope in this research came with the emergence of furfural even in small quantities. Not that we envisaged its future as it is today, but rather as something definitely new and interesting to work with, to dream about, and to hope for.

Again in retrospect, we think there can be little doubt that the *realization* that *furfural was important* was our most vital concept in the early research.

In those days, too, there was always the pressing need for more knowledge about this new material. Although known for nearly a century, references to it were widely scattered and scanty in their content. The need for an up-to-the-minute summary and review of the literature of these new products was realized as important, urgent, and of great magnitude. This need became continuously more urgent because the growth of furan literature had kept pace with the growth of industry. The real problem was to find authors qualified with the knowledge, experience, ability and time to collect the information and convert it into a single critical and constructive study.

Fortunately, the unfolding of the furfural industry has developed and revealed the joint authors, Dr. F. N. Peters and Mr. A. P. Dunlop, as the men best qualified for the preparation of this work. Both have done basic and trouble-shooting research on furfural for many years. Both have become leaders of research in their own right. Both have made substantial contributions to the literature of furfural. Both have had to reconcile the

apparently irreconcilable facts of much of the early literature on the subject. And both have played a vital part in the development of this new chemical industry and of the science about which they write. Their wide experience of the theoretical and commercial problems has given them an understanding of what needs to be written.

Our long and happy personal relationship with them gives us confidence that their book will meet the needs of those interested in the field of furan chemistry. It is our belief that it will become not only a valuable reference book, but also a source of inspiration to those who dream the chemistry of tomorrow.

Harold J. Brownlee,
Southall, Middlesex, England
Carl S. Miner,
Chicago, Illinois

January, 1953

PREFACE

In the early 'thirties, one of the authors (F. N. P.) undertook to prepare a monograph dealing primarily with furfural and its industrial applications, with a minimum of discussion of the theoretical aspects of its chemistry. Although considerable progress was made over an extended period of time, the press of other matters necessitated many delays and periods of inactivity, so that the task was never completed. Though never actually abandoned, preparation of the manuscript was more or less shelved until about the middle of the year 1947, when the editors of The American Chemical Society Monograph Series reopened the subject.

In the intervening years, the growing interest in the field of furan chemistry strongly suggested that a book of the original scope would no longer suffice. It had become increasingly clear that there was need for considerably more comprehensive treatment of the subject, for more or less encyclopedic coverage of furan compounds with particular attention to the behavior of the furan nucleus. After serious consideration of the greatly magnified problems presented by such a treatise, the authors agreed to proceed in a joint effort, of which this monograph is the result.

Within the framework of our general conclusions with regard to scope, it soon became clear that some curtailment was desirable if for no other reason than to limit the monograph to some reasonable physical size. To include all of the known compounds possessing a five-membered ring comprising four carbon atoms and one oxygen atom borders on the impossible. It would necessitate a book of monumental proportions, encompassing a host of compounds bearing little or no relationship to the furans, including such as maleic, succinic, and *o*-phthalic anhydrides, together with the almost innumerable gamma-lactones. It was early decided to omit discussion of condensed ring systems such as benzofuran, dibenzofuran, and related types wherein a furan ring is fused to another cycle. Later, it became apparent that to include the known dihydrofurans, and particularly, the tetrahydrofurans, would increase the task to somewhat staggering proportions, hence these are largely omitted from the chemistry section of the monograph (Part I) except where they are important to an understanding of the reactions and formation of unsaturated furan types. On the other hand, the commercial importance of tetrahydrofuran and tetrahydrofurfuryl alcohol as chemical intermediates for the synthesis of adiponitrile and dihydropyran, respectively, demanded their inclusion in Part II, which deals with industrial applications.

The monograph should provide a ready source of information for those interested in the chemistry and uses of furan types. If it also provides a stimulus to chemists to fill the many gaps in our present knowledge of the subject, it will, indeed, have been a contribution to this branch of organic chemistry.

In Part I, comprising a total of fifteen chapters, an attempt has been made to draw some more or less general conclusions with reference to the chemical behavior of furan compounds, and to present also a comprehensive review of the published work in the field. Of course, a good deal of the early work has been extended, improved and, in some instances, corrected in subsequent studies. As a consequence, not all of the researches are considered in detail, although as far as possible, all through December, 1950, are included in the references in order to fulfill one of the major objectives, which was to offer a complete and critical examination of the published information. A word about the system of referencing may be in order. Literature references are numbered, within each chapter, in the order of their appearance in the text. On the other hand, on any particular subject, the references cited are, in the best judgment of the authors, listed in the order of their importance to that subject, rather than serially. The complete manuscript was submitted to the editors on January 22, 1952.

Part II, concerned with the applications of furfural and its derivatives, presented many problems. There is scarcely an industry in which the use of a furan compound has not been suggested, either by some of the 3500 patents which have appeared, or in letters which we have received from time to time. Such suggestions run the gamut from comestibles to cosmetics, from soaps to soporifics, and have come from most of the countries of the world. They form the basis for what has been termed "the romance of furfural." But this is not a basis upon which a technical monograph can be constructed. Even a comprehensive survey of the larger industrial outlets must be limited for two reasons: (1) lack of space to include many variations from the principal applications, and (2) reluctance to disclose certain "know how" or "secret processes" which inevitably come to the manufacturer of any widely used raw material. Therefore, much that we would like to include regarding industrial uses of the furans has been eliminated for one or both of the foregoing reasons. Such uses as have been included are described broadly, but with sufficient bibliographical references to enable the reader to quickly locate the literature most pertinent to a particular field. Part II, in manuscript, was submitted to the editors on March 17, 1952.

During the more than four years in which Part I took shape, a number of individuals made important contributions which it is a pleasant duty to acknowledge. Particular thanks are due to Mrs. Alma Anderson Mehn, on whom fell the brunt of the library work and the supervision of the clerical

staff, and to Mrs. Frances B. Aylor, Mr. Matt Ban, and Miss Barbara Anne Wehringer. To Professor Charles D. Hurd, of Northwestern University, the authors are deeply indebted for his untiring efforts in reviewing all of the chapters in manuscript form, and for much helpful advice and criticism. Acknowledgment is made also to Mr. Harold J. Brownlee, whose original manuscript dealing with the production of furfural was freely used as a basis for those sections of Chapter 8 concerned with the historical and industrial development of the aldehyde, and its sources. We also gratefully acknowledge the efforts of Mr. Samuel Swadesh, who contributed Chapter 15; of Dr. Edward Sherman, who collected and edited the physical constants section of Chapter 8; of Mr. Shelbert Smith, who provided the summary from which the physical measurements portion of Chapter 1 was prepared and who, together with Mr. Fred Rice, Jr., assumed the arduous task of proofreading the manuscript. Thanks are due also to Professor C. L. Wilson of The Ohio State University for advice in connection with a number of knotty theoretical points, and for submitting to the authors a manuscript on furan metallic compound from which Chapter 6 was, in large measure, prepared. Others who made some contribution during the course of the work include: Mr. Paul R. Stout, Dr. Louis Schmerling, Dr. George F. Wright, Dr. William B. Stillman, and Mr. P. A. Wells, Jr.

Assistance in the preparation of Part II has come from so many persons, and in so many ways, it is not feasible to note them all individually. Many members of The Quaker Oats Research and Chemicals Departments did library work, abstracting and the like, typing and retyping, and solicited comments from industrial users of furan compounds. Our particular thanks are extended to this group which includes, among others, Mrs. Joyce S. Repetsky, Mr. Floyd Trimble, Mr. Frank F. McKinney, Mr. Edward A. Reineck, Dr. Louis G. Smith, and Mrs. Winifred B. Squire. Certain sections of the original manuscript were reviewed by our friends in industry, but special mention should be made of the assistance given by Mr. William P. Gee, Mr. H. H. Gross, Mr. Arthur Langmeier, and Mr. J. T. Zawodni.

We also wish to express our thanks to the editors of The Journal of the American Chemical Society, Journal of the Chemical Society (London), Journal of Organic Chemistry, Australian Journal of Scientific Research, Transactions of the Faraday Society, Industrial and Engineering Chemistry, Chemical Engineering, and The Journal of the American Pharmaceutical Association, for their kind permission to reproduce miscellaneous tabulated data and diagrams which originally appeared in these various journals.

In retrospect, the authors realize that even with the help received from those indicated above, these pages would never have appeared in print without the aid of certain persons who wrote no chapters, corrected no

manuscript, nor read any copy. We refer first to the executive officers of The Quaker Oats Company who permitted us to write the book, and made available a large amount of typing, clerical and library assistance. Another, and possibly the greatest source of help, we now acknowledge. This is the spiritual aid, the comforting words, the sacrifice of social contacts, the job of keeping the children quiet, the spectacle of reams of manuscript all over the house, all uncomplainingly given over a number of years by our wives. No one who is not, simultaneously, a husband, father and author can appreciate how deeply grateful we are for this help, the more so since there can be no adequate recompense.

Chicago, Ill.
January, 1953

A. P. Dunlop
F. N. Peters

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PART I

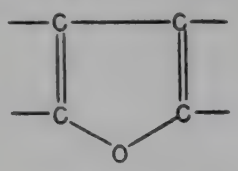
THE CHEMISTRY OF THE FURANS

Chapter 1

THE FURAN SERIES OF CHEMICAL COMPOUNDS

Introduction

Furan compounds belong to that class of substances possessing heterocyclic nuclei. Specifically, the furan nucleus comprises four carbon atoms and one oxygen, and is generally represented pictorially as:



The parent compound of the series is furan, C_4H_4O, to which a great number of derivatives are directly related in the same way that benzene derivatives are related to benzene, that is, by replacement of one or more hydrogen atoms by other atoms or groups. While there are many points of similarity in the behavior of furan and benzene types, there are also major differences, attributable mainly to the greater reactivity and lesser integrity of the furan nucleus compared to the benzene ring. Thus, furans substitute with greater ease than their benzene analogs and exhibit a greater variety of addition reactions. Special precautions are necessary in many instances in order to retain the identity of the furan ring which is more susceptible to cleavage than is that of benzene. As discussed elsewhere (Chapter 14), however, the ease with which the furan ring is ruptured varies with the nature and number of substituent groups, and certain substituted types are notably stable.

Historically, furan compounds date back to the year 1780 when Scheele[1] obtained furoic acid (pyromucic acid) as a product of the dry distillation of mucic acid. Approximately fifty years later, Dobereiner[2] accidently discovered furfural while preparing formic acid by the action of sulfuric acid and manganese dioxide on sugar. The relationship between the two compounds was established by Schwanert[3] who oxidized furfural with silver oxide to furoic acid and showed furfural to be an aldehyde. At about the same time, Ulrich[4] derived the acid from furfural and alcoholic potassium

[1] Scheele, "Sämtliche Physische und Chemische Werke," Vol. II, p. 265, Berlin, compiled by Hermbstädt (1793); *Beilstein*, XVIII, 272.

[2] Dobereiner, *Ann.*, **3**, 141 (1832).

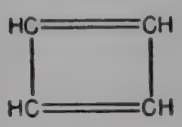
[3] Schwanert, *Ann.*, **114**, 63 (1860); **116**, 257 (1860).

[4] Ulrich, *Chem. News*, **3**, 116 (1861).

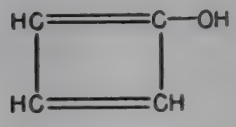
hydroxide, and it was shown later[5] that a third member of the series, furfuryl alcohol, was formed simultaneously under these conditions. Furan itself was first isolated by Limpricht[6] in 1870 by heating barium furoate with soda-lime.

Structure of the Furan Nucleus

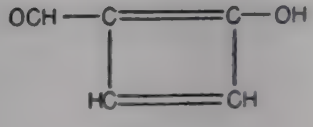
Limpricht[7] (see also [8]) believed furfural and furoic acid to be derivatives of a cyclic hydrocarbon, tetrol (C_4H_4). Accordingly, he assigned to furan the structure of hydroxytetrol and named it "tetraphenol." Similarly, furfural and furoic acid were presumed to be analogs of salicylaldehyde and salicylic acid, respectively, as indicated.



"tetrol"

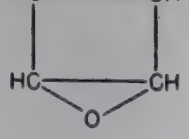


"tetraphenol"

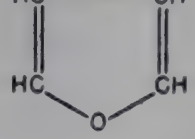


"furfural"

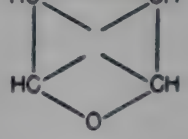
Wichelhaus[9] demonstrated the incorrectness of these formulations, and suggested a ketonic or etheric function for the third oxygen atom of furoic acid. The later studies of Baeyer[10] showed the absence of a carbonyl group, and led him to propose three possible configurations (I, II, and III) for furan. These, he felt, conformed to the known chemical behavior of furan types, that among other things, each was consistent with the early observation of Malaguti[11] that furoic ester adds four atoms of chlorine, and with Limpricht's[5] observation that furoic acid is oxidizable to fumaric acid.



I



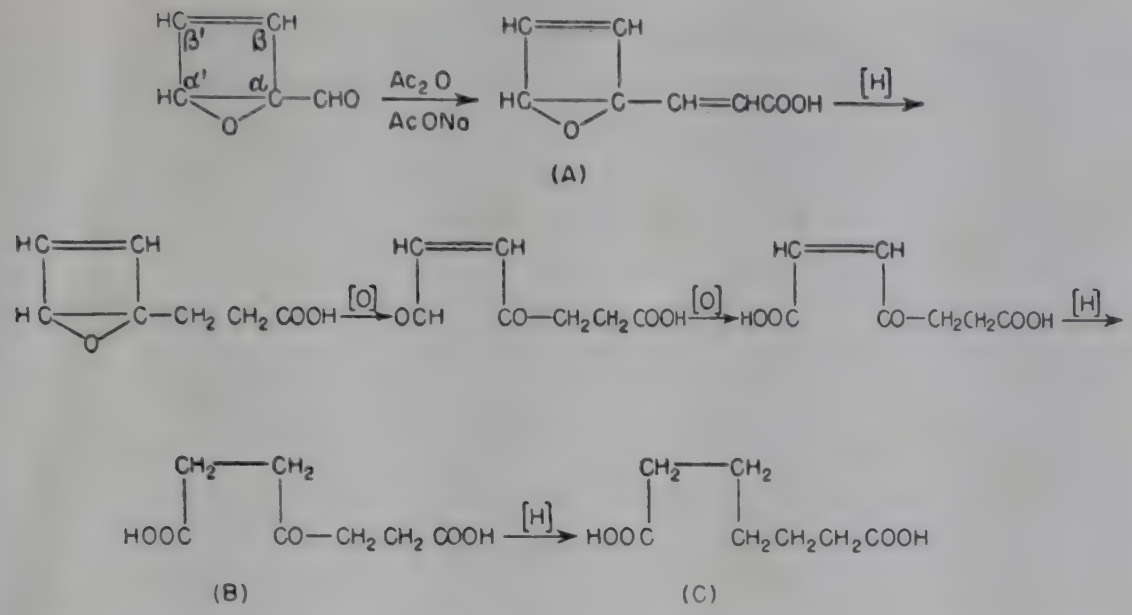
II



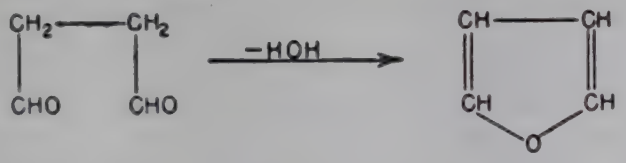
III

To establish the structure of furfural, but particularly to locate the position of the aldehyde group, Baeyer[10] carried out the following reactions. He observed that furfural, like benzaldehyde, reacted in the Perkin condensation to give an unsaturated carboxylic acid, furylacrylic acid (A), from which the known pimelic acid (C) was subsequently derived by the sequence of steps outlined below. Since C is a straight-chain molecule

[5] Limpricht, *Ann.*, **165**, 253 (1873).
[6] Limpricht, *Ber.*, **3**, 90 (1870).
[7] Limpricht, *Ber.*, **2**, 211 (1869).
[8] Schiff, *Ann. suppl.*, **6**, 1 (1868).
[9] Wichelhaus, *Ann.*, **152**, 257 (1869).
[10] Baeyer, *Ber.*, **10**, 355, 695, 1358 (1877).
[11] Malaguti, *Ann. chim. phys.*, (*2*), **64**, 275 (1837).



and not a branched compound, this work established the aldehyde group on an α-nuclear carbon atom. The result was further interpreted by Baeyer in favor of the ethylene oxide structure (I) for the furan ring whereas Marckwald[12, 13] cited a closely related study in support of the diolefin formula, II. Marckwald's work involved cleavage of furylacrylic acid, A, by the action of alcoholic hydrogen chloride. In this manner he obtained an ester of the keto acid, B, and this gave rise to C on subsequent reduction. He pointed out that, on the basis of structure I for the nucleus, the cleavage reaction involves rupture of a C—C bond, whereas formula II requires the more likely fission of a C—O linkage. Also in favor of formula II is Harries'[14] synthesis of furan by refluxing an aqueous solution of succinaldehyde.



Several additional structures have been considered in attempting to arrive at a satisfactory formulation which would account for the chemical behavior of furan compounds; which would explain, for example, the pronounced tendency to undergo alpha substitution reaction on the one hand, and 1,4-type addition reactions on the other. The problem, of course, is related to that encountered with benzene: how to differentiate pictorially between olefinic and so-called aromatic bonds. It is not surprising, therefore, that attempts to resolve the problem resemble those employed in connection with benzene. Thus, for furan, we find partial or latent valence formulae patterned after Thiele's concept, a centric structure conforming

[12] Marckwald, *Ber.*, **20**, 2811 (1887).
[13] Marckwald, *Ber.*, **21**, 1398 (1888).
[14] Harries, *Ber.*, **34**, 1488 (1901).

to Bamberger's "aromatic sextet" hypothesis and the postulate of a dynamic equilibrium among several structures due to oscillation of double bonds, akin to the proposal of Kekulé; see [15]. That is, while furan was recognized as a cyclic compound composed of four atoms of carbon, four of hydrogen, and one of oxygen, there remained the problem of how to depict the valency distribution.

The modern view is that furan is a so-called resonance hybrid.[16, 17] It is proposed that the conventional structure, *i*, is in a state of quantum-mechanical resonance with the several structures (*ii*, *iii*, and *iv*) illustrated below, structures *ii* and *iii*, each representing but one of two configurations which are mirror images, and structure *iv* representing excited structures which are characteristic of the conjugated system C=C—C=C. The energy content of the resonance hybrid is lower than that of the contributing



i ii iii iv

structures, so that the molecule acquires a degree of stabilization (the resonance energy), the magnitude of which has been derived from thermochemical data. Thus, the heat of hydrogenation of furan is 36.6 kcal./mole[18] as compared to 53.8 kcal. for two moles of cyclopentene. The difference, 17.2 kcal., is attributable to resonance, and is in fair agreement with the resonance energy[a] (23 kcal./mole) calculated from combustion data[22].

It is difficult to assess the relative importance of the several structures as contributors to the hybrid molecule. Those represented by *ii*, however, are presumed to be more important than *iii* inasmuch as they involve a smaller separation of charge. Experimental support of this view can be seen in the behavior of furan compounds in substitution reactions. An incoming group is oriented, almost exclusively, to an alpha nuclear carbon atom indicating a relatively high electron density in the alpha position;

[a] For calculation using the method of molecular orbitals, see Bremner and Bremner[19] and Wheland and Pauling[20] (see also[21]).

[15] Gilman and Wright, *Chem. Revs.*, **11**, 323 (1932).

[16] Pauling, "The Nature of the Chemical Bond and the Structure of Molecules and Crystals," 2nd Ed., Ithaca, N. Y., Cornell University Press (1940).

[17] Wheland, "The Theory of Resonance and Its Application to Organic Chemistry," New York, John Wiley and Sons (1944).

[18] Dolliver, Gresham, Kistiakowsky, Smith and Vaughan, *J. Am. Chem. Soc.*, **60**, 440 (1938).

[19] Bremner and Bremner, *J. Chem. Soc.*, **1950**, 2335.

[20] Wheland and Pauling, *J. Am. Chem. Soc.*, **57**, 2086 (1935).

[21] Franklin, *J. Am. Chem. Soc.*, **72**, 4278 (1950).

[22] Schomaker and Pauling, *J. Am. Chem. Soc.*, **61**, 1769 (1939).

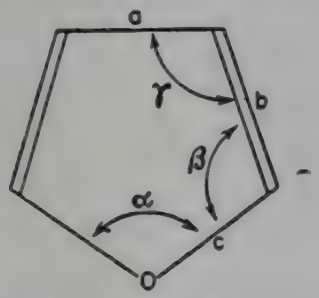
examples of beta substitution of a furan type possessing an available alpha position are very rare. While the structures represented by *iv* would also favor α-substitution, they are considered to make only a very minor contribution to the hybrid because the outer shell of one of the alpha carbon atoms possesses only six electrons. Thus, it would appear that resonance among structures *i* and *ii* is responsible for the greater part of the resonance energy of furan.

As with other resonating molecules, the actual structure of furan cannot be presented pictorially. For purposes of illustration, however, the conventional diolefin formula, *i*, is employed throughout this monograph. Furan may be considered to be a cyclic, dienic ether, modified by resonance.

Physical data which have contributed to an understanding of structure are presented below.

Electron Diffraction

By means of the electron diffraction technique, Schomaker and Pauling[22] (see also [23]) found furan to be a planar molecule with these dimensions:



a	1.46 Å
b	1.35 Å
c	1.41 ± 0.02 Å
α	107 ± 4°
β	109 ± 3°
γ	107 ± 2°

From the measured interatomic distance, they estimated that the C—O linkage possesses 5 ± 5 per cent double bond character, attributable to resonance of structure *i* with structures *ii* and *iii*. Also attributable to this resonance, including the contribution of structure *iv*, is the apparent shortening of the C—C bond (normal value, 1.54 Å), and stretching of the C=C bonds (normal value, 1.34 Å). The total contribution of structures *ii* and *iii* to the resonance hybrid was calculated to be about 10 per cent based on the measured carbon-oxygen distance (compare dipole moment data).

Pyrrole and thiophene were also included in this investigation, and it was concluded that, in these resonating molecules, excited structures corresponding to *ii* and *iii* make a greater contribution (24 and 34 per cent, respectively) to the hybrid molecule than for furan. This is explained in terms of the relative electronegativity of the heteroatom. Oxygen being more electronegative than nitrogen and sulfur, furan is less disposed than pyrrole and thiophene to assume excited electronic states in which the heteroatom acts as an electron donor. The order of increasing resonance stabilization and aromaticity of the three heterocycles is reported: furan < pyrrole < thiophene.

Raman Spectra

It has been confirmed by many investigators that furan does not have the band at 1600 cm.$^{-1}$, characteristic of ethylenic double bonds. Instead, the band due to

[23] Beach, *J. Chem. Phys.*, **9**, 54 (1940).

furan double bonds occurs at about 1485 cm.$^{-1}$. The corresponding band for cyclopentadiene occurs at 1500 cm.$^{-1}$, and for benzene, at 1580 cm.$^{-1}$. According to Truchet and Chapron,[24] these shifts in band spectra are due to oscillation of conjugated double bonds; their work was in agreement with the concept of an aromatic, five-membered ring structure for furan. Bonino[25, 26, 27, 28, 29] similarly concluded that the frequency assignments in furan were in accord with a centric electronic configuration.

Catlin and Wilhelm[30] were concerned with the relative aromaticity of furan, and attempted to correlate its chemical behavior with the displacement of band spectra. They, too, found that the ethylenic bond line was displaced in the furan molecule, but found a band at about 3158 cm.$^{-1}$ which is characteristic of the C=C—H grouping. The intensities of lines between 1559 cm.$^{-1}$ and 1610 cm.$^{-1}$, in furan were weak in the compounds studied, indicative of a shift of the normal ethylenic bond line due to peculiar electronic configurations.

Reitz[31] obtained Raman spectra for furan, pyrrole and thiophene, and called attention to the similarity of these heterocycles. From a study of the depolarization

TABLE 1. RAMAN SPECTRA OF FURAN
Characteristic Bands (cm.$^{-1}$)

Glockler and Wiener[32]	Bonino and Manzoni-Ansidei[25]	Reitz[31]	Catlin and Wilhelm[30]	Médard[33]
—	483	500	—	—
604	609	601	603	610
—	—	—	—	—
735	719	724	730	—
857	842	839	—	—
—	867	871	863	879
—	963	—	—	—
990	985	986	996	—
—	1034	1034	—	1045
1055	1056	1061	1058	1068
1139	1137	1137	1140	1147
—	—	1270	—	—
—	—	1324	—	—
1381	1378	1380	1370	1390
—	—	1457	—	—
1486	1483	1483	1487	1494
—	—	2936	—	—
—	—	3089	—	—
—	3120	3121	—	3128
3165	3160	3154	3158	3163

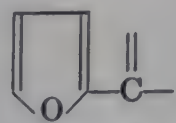
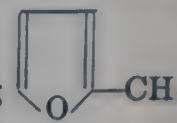
[24] Truchet and Chapron, *Compt. rend.*, **198**, 1934 (1934).
[25] Bonino and Manzoni-Ansidei, *Z. physik. Chem.*, **B, 25**, 327 (1934).
[26] Bonino, *Gazz. chim. ital.*, **65**, 5 (1935); *C. A.*, **29**, 3603 (1935).
[27] Bonino, *Atti accad. Lincei, Classe sci. fis., mat. nat.*, **24**, 374 (1936); *C. A.*, **31**, 4207 (1937).
[28] Bonino and Manzoni-Ansidei, *Ricerca sci.*, **7**, I, No. 7–8, 2 pp. (1936); *C. A.*, **31**, 3388 (1937).
[29] Bonino, *Atti X° congr. intern. chim.*, **2**, 141 (1938); *C. A.*, **33**, 7195 (1939).
[30] Catlin and Wilhelm, *Iowa State Coll. J. Sci.*, **10**, 135 (1936).
[31] Reitz, *Z. physik. Chem.*, **B, 33**, 179 (1936); **B, 38**, 275 (1937).
[32] Glockler and Wiener, *J. Chem. Phys.*, **2**, 47 (1934).
[33] Médard, *Bull. soc. chim.* (*5*), **1**, 934 (1934).

factor and the frequency values, he concluded that the furan molecule was planar and diolefinic in character.

TABLE 2. RAMAN SPECTRA OF FURAN, PYRROLE AND THIOPHENE
Characteristic Bands (cm.$^{-1}$)

Furan[33]	Pyrrole[34]	Thiophene[35]
		375
		453
		565
601		
		604
	621	
		686
	706	
724		
		748
	828	
		832
839		
	852	
		866
871		
		898
986		
		1032
1034		
	1035	
1061		
	1078	
		1079
1137		
	1140	
1171		
1270		
		1358
	1377	
1380		
		1404
	1466	
1483		
		2996
	3073	
		3078
3089		
		3108
3121		
	3123	
3154		
	3380	

[34] Bonino, Manzoni-Ansidei and Pratesi, *Z. physik. Chem.*, **B, 25,** 348 (1934).
[35] Thompson and Temple, *Trans. Faraday Soc.*, **41,** 27 (1945).

In furan types possessing the grouping  (furoic esters, furylacrylic acid and its esters), Han[36, 37, 38] found lines at $\Delta\tilde{\nu}$ 1460 (1480) and 1572. He also reported lines at $\Delta\tilde{\nu}$ 1507 and 1605 as characteristic of the grouping  , as in methylfuran, furfuryl alcohol and furfuryl acetate. On the other hand, furfural and 2-furoyl chloride (see also [39]) were noted to possess lines at $\Delta\tilde{\nu}$ 1460 and 1507. Han explained the occurrence of the latter in these instances using a centric ring structure for the furan nucleus. As characteristic of α-substituted furans (furfuryl ethers, vinylfuran, furfurylideneacetone, 2-furonitrile, etc.), Han[36] reported intense Raman lines at 625, 888, 925, 1020, 1081, 1153, 1232, 1390, 1460 (1480), 1575 (1605), 3122, 3153 cm.$^{-1}$.

From the Raman spectra of furylacrylic and cinnamic esters in the region $\Delta\tilde{\nu}$ 1400 to 1600, Matsuno and Han[38] concluded in favor of the *trans* configuration for the furan ester and attributed the intense line at 1641 cm.$^{-1}$ to the C=C bond in the side chain. The same line was also noted in 2-vinylfuran.[36, 37]

Lu[40] obtained the Raman spectra of furfural and benzaldehyde, and observed a line at $\Delta\tilde{\nu}$ 1670 which was prominent in both instances. The same line was also found in acetic acid, and was attributed to the carbonyl group. This group, in furfural, has a doublet form; lines at 1669 and 1690 cm.$^{-1}$ were observed by Rolla and Chiorboli,[41, 42] the former being the more intense. The position and persistence of the doublet was unchanged in various solvents although the intensity varied. It was concluded that the higher frequency component of the doublet was due to the C=O group in the unassociated molecule. The lower frequency component was ascribed to intermolecularly associated molecules.

From the observed results, the furan ring has been assigned a C_2, symmetry showing nine Raman lines. This assignment necessarily imposes a planar structure. By comparison of the Raman spectra, it appears that the order of aromaticity in terms of the shift of the characteristic ethylenic bond is: benzene > thiophene > pyrrole > furan.

Infrared Spectra

The earliest infrared spectra of furan was due to Coblentz[43] in 1905. More recently, Bonino,[26, 27, 28, 29] and Manzoni-Ansidei and Rolla[44] have gone to considerable

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[36] Han, *Bull. Chem. Soc. Japan*, **11**, 701 (1936); *C. A.*, **31**, 4901 (1937).

[37] Matsuno and Han, *Bull. Chem. Soc. Japan*, **9**, 327 (1934); *C. A.*, **28**, 7160 (1934).

[38] Matsuno and Han, *Bull. Chem. Soc. Japan*, **12**, 155 (1937); *C. A.*, **32**, 2027 (1938).

[39] Thatte and Joglekar, *Phil. Mag.*, **23**, 1067 (1937).

[40] Lu, *Sci. Repts. Natl. Tsing Hua Univ.*, Ser. **A, 1**, 25 (1931); *C. A.*, **26**, 1515 (1932).

[41] Rolla and Chiorboli, *Gazz. chim. ital.*, **79**, 513 (1949); *C. A.*, **43**, 8888 (1949).

[42] Rolla and Chiorboli, *Boll. sci. facoltà chim. ind. univ. Bologna*, **7**, 26 (1949); *C. A.*, **43**, 8888 (1949).

[43] Coblentz, "Investigations of Infrared Spectra," Carnegie Institution of Washington, Publication No. 35, Washington, D. C., Henry E. Wilkens Printing Co. (1905).

[44] Manzoni-Ansidei and Rolla, *Atti accad. Lincei, Classe sci. fis. mat. nat.*, **27**, 410 (1938); *C. A.*, **32**, 8933 (1938).

lengths in attempting to explain several infrared bands which appeared to have no counterpart in the Raman spectra. According to Garach and Lecomte,[45, 46] this seeming discrepancy was due to the low intensities observed in the earlier work. They further point out that a planar molecule with C_{2v} symmetry adequately explains the observed data. This was confirmed by Thompson and Temple[35] using an instrument of very high resolving power. Their results (Table 2) agree with the Raman data and infrared data of other investigators. Moments of inertia were computed from the bond angle data of Schomaker and Pauling,[22] and frequency assignments were made according to the various vibrations. The furan molecule is described as a symmetrical rotator with two equal moments of inertia. In the infrared spectra, eight bands are found due to ring deformation, six bands due to C—H bending, and four bands due to C—H stretching. Thompson and Temple[35] argued that if furan were non-planar, observed Raman and infrared spectra would differ, whereas comparison showed excellent agreement. The only symmetry assignment which reconciles this concordance is C_{2v}, hence furan is a planar molecule.

TABLE 3. INFRARED SPECTRA OF FURAN, PYRROLE AND THIOPHENE[35]

Class	Type	Pyrrole	Furan	Thiophene
A_1	ring	711	724	604
	C—H deformation	1076	1067	1032
	ring	1144	994	832
	C—H deformation	1237	1137	1077
	ring	1384	1381	1358
	ring	1467	1486	1404
	C—H stretching	3100	(3090)	(3080)
	C—H stretching	3133	(3120)	(3110)
	N—H stretching	3400	absent	absent
A_2	ring	(510)		
	C—H deformation	711	?, ?, ?	?, ?, ?
	C—H deformation	868		
B_1	ring	647		
	C—H deformation	1015	872, 1270	872, 1252
	C—H deformation	1046	?, ?	?, ?
	ring	1418		
	ring	1530	1579	1590
	C—H stretching	3111	(3090)	(3080)
	C—H stretching	(3133)	(3120)	(3110)
	N—H deformation	(1146)	absent	absent
B_2	N—H deformation	565	absent	absent
	C—H deformation	768		
	ring	838	605, 744	710, ?, ?
	C—H deformation	(1046)	837	
	probable fundamentals unallocated		1034	686, 748 453, 565

[45] Garach and Lecomte, *Compt. rend.*, **222**, 74 (1946).
[46] Lecomte, *Bull. soc. chim. France*, **1946**, 415.

A number of combinations and overtones are found in the infrared spectra of furan. Resolution of some of these bands has been reported by Pickett[47] (see also [25]) in connection with a study of furan and pyrrole in the vapor state. These heterocycles showed very similar characteristics. The following lines were ascribed to the furan nucleus: 624, 725, 872, 1139, 1389, 1490 and 1580 cm.$^{-1}$; those due to C—H bending were reported to be 763, 999, 1073 and 1264 cm.$^{-1}$. Of the number of vibrations expected, assuming C_2, symmetry, three bands (one due to the nucleus, and two to C—H stretching) are inactive in the infrared. A very strong band at 1580 cm.$^{-1}$, was observed which has no counterpart in either Raman or infrared spectra in the liquid state. A band in this region (1600 cm.$^{-1}$, is characteristic of the ethylenic bond) might be expected, however, in the vapor state.

A marked similarity has been observed in the infrared spectra of furfural, furfuryl alcohol and hydrofuramide.[48] In the region 10–11 μ, a band due to the C—C linkage was found in each instance. Bands were also noted in the region 5.6 to 6.6 μ, and ascribed to vibrations of C=O, C=C, and C=N linkages. Mulliken[49] has discussed the effect of hyperconjugation on the infrared spectra of furan types. For attempted correlation of the shift of the infrared band of the O—D linkage in deuteromethanol containing furan compounds, see Gordy and Stanford.[50, 51] Blout, Fields and Karplus[52] have reported on the infrared spectra of 2-furylalkenals and their azine derivatives.

Visible and Ultraviolet Spectra

The absorption of furans in the visible and ultraviolet regions has been studied primarily for its value in the identification of particular compounds, or of groups within the molecule. The simpler furans do not show selective absorption[53, 54, 55]; hence, most of the studies have been directed toward an examination of substituted furans in which the substituent forms a conjugated system with the nucleus. This conjugation shifts the absorption bands toward the visible and ultraviolet regions of the spectrum; the intensity of this absorption is generally increased by an increase in the extent of conjugation. The main absorption bands for a variety of furan types are listed in Table 4.

The effect of polar and unsaturated substituents was observed by Hughes and Johnson,[62] who compared the wave length and extinction coefficients of furan, 2-vinylfuran, furfural, and 3-(2-furyl)acrylic acid and its ethyl ester. Furan itself, and derivatives wherein substituent groups are incapable of conjugation with the

[47] Pickett, *J. Chem. Phys.*, **10**, 660 (1942).
[48] Rogers and Williams, *J. Am. Chem. Soc.*, **60**, 2619 (1938).
[49] Mulliken, *J. Chem. Phys.*, **7**, 339 (1939).
[50] Gordy and Stanford, *J. Chem. Phys.*, **8**, 170 (1940).
[51] Gordy and Stanford, *J. Chem. Phys.*, **9**, 204 (1941).
[52] Blout, Fields and Karplus, *J. Am. Chem. Soc.*, **70**, 194 (1948).
[53] Boryniec and Marchlewski, *Bull. intern. acad. Polonaise*, **1931, A**, 392; *C. A.*, **27**, 229 (1933).
[54] Abe, *J. Chem. Soc. Japan*, **55**, 901 (1934); *C. A.*, **29**, 405 (1935).
[55] Hartley and Dobbie, *J. Chem. Soc.*, **73**, 598 (1898).
[56] Mackinney and Temmer, *J. Am. Chem. Soc.*, **70**, 3586 (1948).
[57] Hofmann, *J. Am. Chem. Soc.*, **66**, 51 (1944).
[58] Kasiwagi, *Bull. Chem. Soc. Japan*, **I**, 145 (1926); *C. A.*, **21**, 86 (1927).
[59] Menczel, *Z. physik. Chem.*, **125**, 161 (1927).
[60] Heilbron, Jones, Smith and Weedon, *J. Chem. Soc.*, **1946**, 54.
[61] Johnson, *J. Chem. Soc.*, **1946**, 895.
[62] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).

TABLE 4. ABSORPTION BANDS OF SOME FURAN TYPES IN VISIBLE AND ULTRAVIOLET REGION

Compound	λ maxima (mμ)	log ε	Ref.
Furan	250	3.4	57
	267	—	58
	251.6, 261.3, 274.7, 281.3	−0.90, −0.35, −0.58, −0.757	59
	290, 270	1.4, 0.8	56
(for homologs of, see [60, 61, 62, 63])			
Furfuryl alcohol	263.1, 208, 220	2.0, 3.8, 0.95	59
	268	—	58
	275	—	67
	279.8, 264.4, 245	1.89, 2.04, 1.8	59
	280, 250	−2.48, −2.0	56
Furfural	267.8, 277.8, 333	3.84, 3.75, 1.5	59
	268, 334.5	4.29, $>1.4<1.73$	72
	270, 313	4.17, 1.78	69
	270	—	74
	272	—	74, 75
	277, 227	4.18, 3.61	68
	277	4.16	70, 71
	277.5, 240, 230	4.7, 3.17, 3.36	56
	278	4.16	73
	279, 226	—	67
Furfural oxime, *syn*	270	4.24	65
Furfural oxime, *anti*	265	4.25	65
	265	4.2	77, 78, 79
(for other derivatives, see[80, 81, 82, 67, 97])			
5-Nitrofurfural oxime, *syn*	230, 345	4.08, 4.097	65
5-Nitrofurfural oxime, *anti*	230, 340	3.98, 4.10	65
5-Methylfurfural	280	—	70
5-(Hydroxymethyl)furfural	282.5, 245, 228	4.23, 3.01, 3.28	56, 71
	283	4.16	83, 84
	284, 230	4.22, 3.49	73
	285, 228	4.22, 3.56	68, 85
(for derivative, see[81])			
Oxybis(5-methylenefurfural)	282.5, 245, 230	4.23, 3.72, 3.78	56
Miscellaneous furylalkenals:			
C_4H_3O—$(CH{=}CH)_nCHO$, $n = 1$	314, 312	—, 4.42	75, 76, 69
" $n = 2$	350, 346	—, 4.47	75, 76, 69
" $n = 3$	373	—	75, 76
	360, 366, 382	3.72, 4.43, 4.39	69
" $n = 4$	282, 389	3.91, 4.69	69
" $n = 5$	260, 300, 412	3.90, 3.91, 4.86	69
" $n = 6$	280, 320, 429	3.98, 3.80, 4.92	69
2-Furyl methyl ketone	267	—	54, 86
Furfurylacetone	266	—	58

TABLE 4—*Continued*

Compound	λ maxima (mμ)	log ε	Ref.
Furfurylideneacetone	314	—	58, 62
	310	4.34	
(for related types, see [87, 88, 89, 90, 91, 80])			
Difurfurylideneacetone	451	—	92; see also 58
Difurfurylidenecyclopentanone	462	—	92
Furil	302.5, 255, 227.5	4.24, 3.65, 3.97	56
Furoic acid	245, 215	4.06, 3.66	56
	245	—	93
	246	—	67
	248	—	64, 62
	260, 265.5	—, 3.9	59
Furamide	255, 225	4.087, 3.68	56
Furanilide	273	4.3	77, 78, 79
o-Furotoluide	261.5	4.3	77, 78, 79
5-Chlorofuroic acid	256	—	64
3-Chlorofuroic acid	255	—	64
2,5-Furandicarboxylic acid	262.5	4.55	94
Methyl 5-methyl-2,4-furandicarboxylate	262	—	95
3-(5-Phenyl-2-furyl)propionic acid	287, 238	4.26, 3.27	96; see also 98
5-(3,4-Dicarboxy-2-furyl)valeric acid	270	3.4	57
Miscellaneous furylalkenoic acids:			
C_4H_3O—$(CH{=}CH)_n$COOH, $n = 1$	300, 306	—	76
	306	4.70	64, 76
	306.9	4.70	94; see also 62, 64
$n = 2$	320, 337	—	76
$n = 3$	353, 357, 373	—	76

[63] Laitinen, Miller and Parks, *J. Am. Chem. Soc.*, **69**, 2707 (1947).
[64] Dann, *Chem. Ber.*, **80**, 435 (1947).
[65] Raffauf, *J. Am. Chem. Soc.*, **68**, 1765 (1946).
[67] Marchlewski and Mayer, *Bull. intern. acad. Polonaise*, **1929, 3, A,** 169; *C. A.*, **24**, 2052 (1930).
[68] Wolfrom, Schuetz and Cavalieri, *J. Am. Chem. Soc.*, **71**, 3518 (1949).
[69] Blout and Fields, *J. Am. Chem. Soc.*, **70**, 189 (1948).
[70] Fuchs, *Monatsh.*, **81**, 70 (1950); *C. A.*, **44**, 8825 (1950).
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[72] Bielecki and Henri, *Ber.*, **47**, 1690 (1914).
[73] Singh, Dean and Cantor, *J. Am. Chem. Soc.*, **70**, 517 (1948).
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[75] König, *Ber.*, **58**, 2559 (1925).

ring, show negligible absorption. Small extinction coefficients are observed with 3-(2-furyl)propionic acid, furfuryl alcohol, 2-methylfuran and the like.[54, 86]

Furfural exhibits marked absorption in the neighborhood of 270 mμ[99, 100] (see also [55, 72]). Two bands appearing in this region, one at 270 mμ with a large extinction coefficient, and another at 280 mμ with a low extinction coefficient, can be attributed to the nucleus and the carbonyl group, respectively. Recent workers[69, 70, 101, 102, 59, 56, 103] have confirmed this selective absorption of furfural in the ultraviolet.

Dobrinskaya *et al.*[104] (see also [72]) investigated the spectra of furfural in alcohol at several pH levels. At pH 2–5, one single absorption band was found (270 mμ). At pH 12.8, the entire absorption curve was displaced to a lower absorption coefficient with a maximum at about 340 mμ, which band was absent in neutral or acidic solutions. It was concluded that furfural existed in two forms (compare Raman spectra of furfural[41, 42]); the equilibrium constant for the two forms is reported as: $K = \alpha/\beta[H^+]^2 = 5 \times 10^{-9}$, where the α-form is that appearing at pH 2–5, and the β-form is that appearing at pH 12.8. The absorption at 340 mμ is considered to be due to the contribution of resonating structures to the normal aldehyde form which shows up at 270 mμ.

The observed, slight shift in absorption band of 5-methylfurfural as compared to furfural may be attributed to a hyperconjugative effect between the methyl group and the nucleus, inasmuch as the small increase in molecular weight in the former instance should have little or no effect. With 5-(hydroxymethyl)furfural, however,

[76] Hausser, Kuhn, Smakula and Deutsch, *Z. physik. Chem.*, **B, 29,** 378 (1935).
[77] Grammaticakis, *Compt. rend.*, **226,** 729 (1948).
[78] Grammaticakis, *Bull. soc. chim. France*, **1948,** 979.
[79] Grammaticakis, *Bull. soc. chim. France*, **1949,** 410.
[80] Braude and Jones, *J. Chem. Soc.*, **1945,** 498.
[81] Stadtman, *J. Am. Chem. Soc.*, **70,** 3583 (1948).
[82] Blout and Gofstein, *J. Am. Chem. Soc.*, **67,** 13 (1945).
[83] Scallet and Gardner, *J. Am. Chem. Soc.*, **67,** 1934 (1945).
[84] Middendorp, *Rec. trav. chim.*, **38,** 1 (1919).
[85] Haas, Stadtman, Stadtman and Mackinney, *J. Am. Chem. Soc.*, **70,** 3576 (1948).
[86] Abe, *J. Chem. Soc. Japan*, **59,** 1117 (1938); *C. A.* **33,** 2033 (1939).
[87] Maxim and Foscaneanu, *Bucharest*, **1947,** 28 pages; *C. A.*, **42,** 4433 (1948).
[88] Maxim and Foscaneanu, *Compt. rend. acad. sci. Roumaine*, **8,** 70 (1946–1947); *C. A.*, **42,** 5342 (1948).
[89] Maxim and Popescu, *Bull. soc. chim.*, (*5*), **5,** 49 (1938).
[90] Maxim and Copuzeanu, *Bull. soc. chim.*, (*5*), **5,** 57 (1938).
[91] Heilbron, Johnson and Jones, *J. Chem. Soc.*, **1939,** 1560.
[92] Stobbe and Haertel, *Ann.*, **370,** 99 (1909).
[93] Löw, *Acta Chem. Scand.*, **4,** 294 (1950).
[94] Sorensen, *Ann.*, **546,** 57 (1940).
[95] Jones, *J. Chem. Soc.*, **1945,** 116.
[96] Elpern and Nachod, *J. Am. Chem. Soc.*, **72,** 3379 (1950).
[97] Asahina, *Bull. Chem. Soc. Japan*, **4,** 202 (1929); **5,** 354 (1930); *C. A.*, **24,** 298 (1930); **25,** 1508 (1931).
[98] Turner, *J. Am. Chem. Soc.*, **71,** 612 (1949).
[99] Purvis, *J. Chem. Soc.*, **97,** 1648 (1910).
[100] Getman, *J. Phys. Chem.*, **28,** 397 (1924).
[101] Berton, *Ann. chim.*, **19,** 394 (1944).
[102] Berton, *Bull. soc. chim. France*, **1949,** 759.
[103] Walsh, *Trans. Faraday Soc.*, **42,** 62 (1946).
[104] Dobrinskaya, Neiman, Polkanova and Protsenko, *Doklady Akad. Nauk S. S. S. R.*, **63,** 549 (1948); *C. A.*, **43,** 2865 (1949).

the shift to the red region of the spectrum is sizeable (*ca.* 6–15 mμ).[73, 70] The intense band of this aldehyde in the ultraviolet[56, 84, 83] may be related to the auxochromic properties of the hydroxyl group, and to bathochromic effects.[105]

The observed absorption band of furfuryl alcohol at about 275 mμ is accompanied by a very small absorption coefficient. The alcohol has been reported not to show any selective absorption in the ultraviolet.[53, 54, 86, 59] From his studies, Fukumoto[106] attempted to correlate the absorption data with the Raman spectra and the dissociation energy (calc'd. 126.2 kcal./mole).

Furoic acid shows a band with a maximum at about 245 mμ, accompanied by strong absorption and a large absorption coefficient. The latter is appreciably lower than that of furfural, however, although both possess the same chromophore in the same position. The difference is ascribed to the stabilizing effect of the carboxyl group, and perhaps also to intramolecular hydrogen bonding.[107]

Asahina[97] studied the absorption spectra of the azlactones of furfural and benzaldehyde. Though very similar, the furan derivative was observed to be more bathochromic and hyperchromic (see [92, 58, 54, 86, 53]); similar trends have been observed in comparing other furan types with their benzene analogs. Thus, furans show a shift toward lower frequencies, indicating less resonance than the corresponding benzene derivatives. A related effect was noted by Maxim and Copuzeanu[90] (see also [87, 88, 89]) who compared the halochromic properties of furan, pyrrole and benzene types, and reported the furans to be the least stable. Maxim *et al.*[87, 88, 89, 90] likened the furan nucleus to an acyclic conjugated system. They concluded, however, that furan was not entirely acyclic in nature since introduction of a furyl group into an acyclic conjugated compound shifts the absorption band only about one-half as much as the shift observed by introducing an acyclic conjugated group into furan. This observation is similar to the findings of Blout, Fields and Karplus[52] (see also [75]) in connection with infrared studies with α-furylalkenals and their derivatives.

Blout and Gofstein[82] compared the absorption spectra of furfuralazine and benzalazine. The maximum band in the former occurs at about 335 mμ, which is about 35 mμ displacement compared to benzalazine. This was attributed to a larger contribution of dipolar structures to resonance in furfuralazine, as a consequence of the nuclear oxygen atom. A similar study with α-furylalkenalazines showed related effects[69] (see also [76]). For the behavior of α-furylalkenoic acids, see Hausser *et al.*[76]

Johnson[61] employed absorption data to distinguish between the isomeric 2- and 3-*p*-chlorophenylfurans. In the 3-isomer, the unsaturation in the substituent is in conjugation only with the 2,3-double bond of the furan nucleus, whereas the conjugation is more extended in the 2-isomer. Accordingly, the latter should, and does show an absorption band at longer wave length than the 3-isomer. Hughes and Johnson[62] report that α-substituted furans have a molecular absorption coefficient which is consistently higher than the corresponding β-isomers. Absorption data were useful in distinguishing between the *cis* and *trans* isomers of furfural oxime[65] (see also [108]).

To date, few investigations have been carried out with furan types in the Schumann region. Pickett[109] did study furan in this region, however, and found 22 bands in three band systems. The first system contains three bands similar to those observed with cyclopentadiene. In the third system are found three total symmetrical vibrations which are due to the contribution of excited states to the molecule; a

[105] Bowden, Braude and Jones, *J. Chem. Soc.*, **1946**, 948.

[106] Fukumoto, *Sci. Repts. Tohoku Imp. Univ.*, First Ser., **25**, 1162 (1937); *C. A.*, **31**, 5273 (1937).

[107] Ubbelohde, *Proc. Roy. Soc. London*, **A, 152**, 378 (1935).

[108] Ramart-Lucas, Hoch and Klein, *Compt. rend.*, **232**, 336 (1951).

[109] Pickett, *J. Chem. Phys.*, **8**, 293 (1940).

vibrational analysis of furan is possible from this system, the results being indicative of a planar, diolefinic structure modified by resonance. Walsh[103] studied furfural in the Schumann region and reported a Rydberg series of vibrational frequencies similar to those in furan.

Dipole Moment

Using a value of 0.71 D for the dipole moment of furan at 25°, Smyth and Walls[110] calculated the valence angles and concluded that the furan ring has a planar configuration. At 20°, values of 0.63 D[111] and 0.67 D[112] have been reported. Schomaker and Pauling[22] used the latter value to calculate the resonance moment of furan and from this, the resonance energy. The results corresponded to approximately 15 per cent contribution of excited states *ii* and *iii* to the resonance of furan. The resonance energy (14.4 kcal./mole) was also calculated from the dipole moment (0.71 D) by Nazarova and Syrkin,[113] who also determined the dipole moments of a number of substituted furans, and discussed the significance of these data to the question of structure.

In connection with their attempts to correlate solubility characteristics with dipole moments, Fischer and Ehrenberg[114] discussed furan, pyrrole and thiophene in terms of the nucleophilic properties of the heteroatoms.

Table 5. Dipole Moments of Furan Derivatives

Compound	Dipole moment at 25° (Debye units)	Ref.
2-Methylfuran	0.74	113
2-Bromofuran	1.46	113
3-Bromofuran	0.91	113
2,5-Dibromofuran	1.63	113
2,3-Dibromofuran	1.53	113
2-Iodofuran	1.03	113
2-Nitrofuran	4.41	113
2,5-Dinitrofuran	3.93	113
5-Nitro-2-methylfuran	4.91	113
2-(2-Nitrovinyl)furan	5.07	113
Furfuryl alcohol	1.92	113
Furfural	3.57,* 3.61*	115, 116
5-(Ethoxymethyl)furfural	3.45	117
Furil	3.15	113
2-Furoic acid	1.38	113
5-Bromo-2-furoic acid	2.19	113
4-Bromo-2-furoic acid	1.03	113
5-Nitro-2-furoic acid	4.09	113

* No temperature cited.

[110] Smyth and Walls, *J. Am. Chem. Soc.*, **54**, 3230 (1932).
[111] Hunter and Partington, *J. Chem. Soc.*, **1931**, 2062.
[112] de Vries Robles, *Rec. trav. chim.*, **58**, 111 (1939).
[113] Nazarova and Syrkin, *Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk*, **1949**, 35; *C. A.*, **43**, 4913 (1949).
[114] Fischer and Ehrenberg, *Acta Chem. Scand.*, **2**, 669 (1948).
[115] Hassel and Naeshagen, *Z. physik. Chem.*, **B, 6**, 441 (1930).
[116] Shott-L'vova and Syrkin, *J. Phys. Chem. U. S. S. R.*, **12**, 479 (1938); *C. A.*, **33**, 4839 (1939).
[117] Bredereck and Fritzsche, *Ber.*, **70**, 802 (1937).

Parachor

Parachor (Sugden) values, which have been determined for a number of furan types, are in reasonably good agreement with the calculated values, assuming the diolefin (*i*) structure for the furan ring.

TABLE 6. PARACHORS OF SOME FURAN COMPOUNDS

Compound	Parachor observed	Parachor calculated	Ref.
Furan	160.4	162.5	118
2-Methylfuran	199.8	201.5*	118
2,5-Dimethylfuran	240.6	240.5*	118
2-Vinylfuran	233.6	227.6	120
2-Bromofuran	212.6	213.4*	118
2-Nitrofuran	220.8	221.1*	118
Furfuryl alcohol	216.9	221.5*	118
Furfuryl methyl ether	260.8	260.5*	118
Phenylfurfurylamine	397.5	404.0	121
Ethylphenylfurfurylamine	473.5	482.0	121
Furfural		210.5	122, 123
	212.5		118
	212.9		124, 123
	210.1		125
	209.5(20°)		122
	209.4(32.4°)		122
	210.1(42.4°)		122
Ethyl 2-furoate	309.6	305.3*	118
Furfuryl 2-furoate	398.9	394.6*	118

* Calculated using Sugden's atomic parachors.[119]

Molecular Refraction

A definite exaltation is apparent in comparing observed and calculated values for the molecular refraction of furan types.[126, 127, 62, 128, 124, 129] The calculated value, based on the diolefin ring structure (*i*), generally shows a negative exaltation, as in the case of furan itself and those derivatives where there is no conjugation between the ring and a substituent group.[62] Where such conjugation does exist, the exaltation tends to be positive.

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[118] Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935).

[119] The Quaker Oats Company, unpublished data.

[120] Breault and Dermer, *Proc. Oklahoma Acad. Sci.*, **28**, 82 (1948); *C. A.*, **43**, 2615 (1949).

[121] Umnova, *J. Gen. Chem. U. S. S. R.*, **10**, 569 (1940); *C. A.*, **34**, 7902 (1940).

[122] Hartley and Linnell, *Quart. J. Pharm. Pharmacol.*, **11**, 714 (1938).

[123] Sugden, *J. Chem. Soc.*, **125**, 1167 (1924).

[124] Michaels, Alexander and Becker, *Ind. Eng. Chem.*, **42**, 2332 (1950).

[125] Ray, *J. Indian Chem. Soc.*, **11**, 499 (1934).

[126] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta Phytochim.*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).

[127] Henze, Whitney and Eppright, *J. Am. Chem. Soc.*, **62**, 565 (1940).

[128] Kasiwagi and Abe, *J. Chem. Soc. Japan*, **50**, 677 (1929); *C. A.*, **25**, 5674 (1931).

[129] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).

The degree and direction of the exaltation for a variety of furans is shown in Table 7. The small increase in exaltation observed in the series methyl, ethyl and propyl furoate, and in comparing furan with 2-methylfuran and 2,5-dimethylfuran has been attributed by Mulliken[19] to the effect of hyperconjugation. Small differences are also noted between the 2- and 3-isomers of methyl-, chloro- and bromofuran; in each instance, the 2-isomer has a less negative exaltation than the corresponding 3-isomer, thereby offering one means of differentiation. Additional references dealing with the molecular refraction of furan types are[117, 113, 94, 130, 131, 132, 133, 134, 135, 136, 137, 110, 138].

TABLE 7. EXALTATION OF MOLECULAR REFRACTION OF SOME FURAN TYPES

Compound	Exaltation (MR_D (obs.) − MR_D (calc'd.))	Ref.
Furan	−0.761	62
2-Methylfuran	−0.462, −0.21	62, 127
3-Methylfuran	−0.96	126
2,5-Dimethylfuran	−0.239	62, 139
2-Vinylfuran	+1.63	62
2-Chlorofuran	−0.628, −0.65	62, 129
3-Chlorofuran	−0.891, −0.84	62, 129
2-Bromofuran	−0.825, −0.84	62, 129
3-Bromofuran	−1.078, −1.11	62, 129
3,4-Dichlorofuran	−1.10	129
2,3,4-Trichlorofuran	−0.88	129
Furfuryl alcohol	−0.450, −0.45, −0.41	62, 140, 128
Furfuryl acetate	−0.769	62
Furfural	+1.61, +1.66	62, 141, 142
Furfurylideneacetone (4-furyl-3-buten-2-one)	+5.523	62
Furfurylidenemethyl ethyl ketone (1-furyl-1-penten-3-one)	+4.824	62
Furfurylidenepinacolone	+5.524	62
Furfurylacetone (4-furyl-2-butanone)	−0.134	62
1-Furyl-3-pentanone	−0.199	62
Ethyl 3-(2-furyl)acrylate	+4.481	62
Ethyl 3-(2-furyl)propionate	−0.451	62
2-Furonitrile	+0.89	62
Methyl 2-furoate	+0.825	62, 143
Ethyl 2-furoate	+0.921	143
Propyl 2-furoate	+0.948	62, 144
Ethyl 5-chloro-2-furoate	+1.384	62
Ethyl 3-chloro-2-furoate	+0.814	62
Ethyl 2-methyl-3-furoate	−1.04	62
Ethyl 2,5-dimethyl-3-furoate	+0.693	62, 145

[130] Monoya, *J. Pharm. Soc. Japan*, **447**, 357 (1919); *C. A.*, **13**, 2516 (1919).
[131] von Auwers and Ottens, *Ber.*, **57**, 446 (1924).
[132] Ivanov, *Bull. soc. chim.* (*4*), **35**, 1658 (1924).
[133] Fujita, *J. Pharm. Soc. Japan*, **519**, 456 (1925); *C. A.*, **20**, 412 (1926).
[134] Neish and Macdonald, *Can. J. Research*, **25**, B, 70 (1947).
[135] Salmi and Jansson, *Suomen Kemistilehti*, **12**, B, 28 (1939); *C. A.*, **34**, 423 (1940).
[136] Conduché, *Ann. chim. phys.* (*8*), **13**, 94 (1908).

Magnetic Susceptibility

The constants of Pascal[146] for atomic, group and linkage susceptibilities were derived from the magnetic susceptibilities of a large number of compounds, among which was furfural. Since then, the magnetic susceptibility of several additional furans has been determined; the values obtained are listed in Table 8. Comparison of the values obtained with furan, pyrrole and thiophene[147, 148, 149, 150, 151] indicate that furan is less aromatic than the other two heterocycles. For a qualitative correlation of magnetic susceptibility with structure and electronic configuration, see Gray and Cruickshank[152]. The lower value obtained for furoin as compared to furfural has been interpreted[148] as evidence for a free radical mechanism in the formation of furoin from the aldehyde.

TABLE 8. MAGNETIC SUSCEPTIBILITY OF SOME FURANS

Compound	Molecular magnetic susceptibility [($\chi_{mol.} \times 10^{-6}$) c.g.s. units]	Ref.
Furan	−43.09, −43.1, −43.18	147, 153, 150
2,5-Dimethylfuran	−66.04, −66.37	153, 150
Furfuryl alcohol	−60.07	153
Furfurylamine	−63.53	153
Furfural	−47.1, −49.2, −49.8	150, 146, 148
Furoin	−45.6	148

ISOMERISM

Unlike the situation with benzene, the heteroatom in furan imposes a condition of asymmetry which makes possible the existence of two isomeric monosubstitution products. This is clearly expressed by the diolefin structure for the nucleus, which contains two equivalent α-positions (2 and 5) and two equivalent β-positions (3 and 4), but which also indicates the non-equivalence of the α- and β-positions. It follows that, for example, there

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[137] Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 66, 90 (1926); **2**, 310 (1927); *C. A.*, **20**, 2491, 3004 (1926); *C. A.*, **22**, 778 (1928).

[138] von Auwers, Boennecke, Krollpfeiffer and Peters, *Ann.*, **408**, 212 (1915).

[139] Nasini and Carrara, *Gazz. chim. ital.*, **24, I**, 256 (1894).

[140] Wienhaus, *Ber.*, **53**, 1656 (1920).

[141] Brühl, *Ann.*, **235**, 1 (1886).

[142] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany (1930).

[143] von Auwers, *Ber.*, **44**, 3679 (1911).

[144] Gennari, *Gazz. chim. ital.*, **24, I**, 246 (1894).

[145] Brühl, *J. prakt. Chem.*, **50**, 119 (1894).

[146] Pascal, *Bull. soc. chim.* (*4*), **9**, 134 (1911).

[147] Bonino and Manzoni-Ansidei, *Ber.*, **76**, 553 (1943).

[148] Bhatnagar, Nevgi and Mathur, *Z. Physik*, **100**, 141 (1936); *C. A.*, **30**, 5083 (1936).

[149] Hazato, *J. Chem. Soc. Japan*, **63**, 1685 (1942); **64**, 622 (1943); *C. A.*, **41**, 3334 (1947).

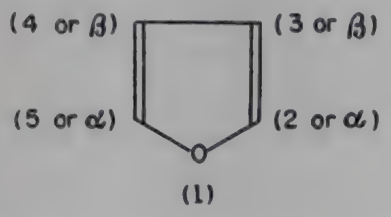
[150] Pacault, *Ann. chim.* (*12*), **1**, 527 (1946).

[151] Preiswerk, *Helv. Phys. Acta*, **7**, 203 (1933); *C. A.*, **28**, 2999 (1934).

[152] Gray and Cruickshank, *Trans. Faraday Soc.*, **31**, 1491 (1935).

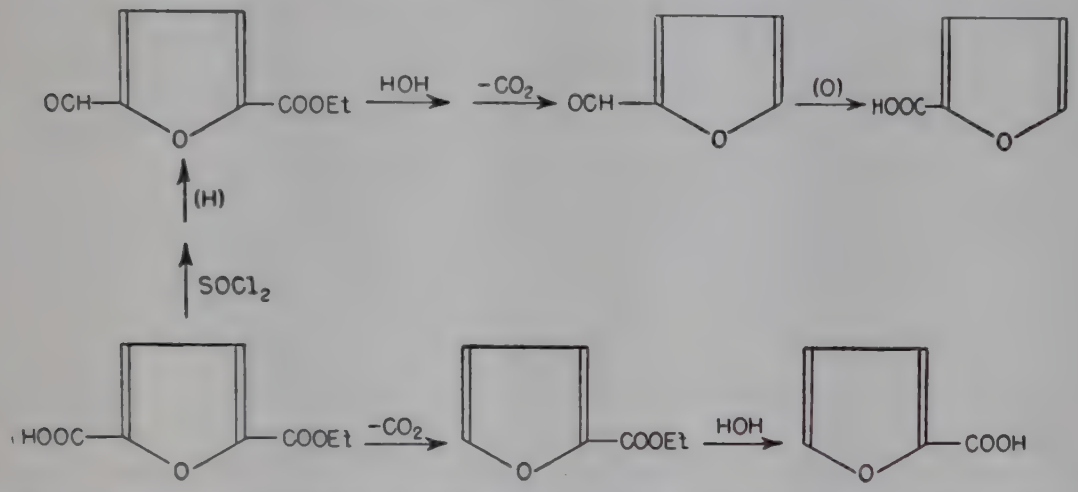
[153] Bonino and Manzoni-Ansidei, *Ricerca sci.*, **7, I**, No. 3–4, 1 p. (1936); *C. A.*, **31**, 3353 (1937).

should be two, but only two monochlorofurans, and this is in agreement with experimental findings.



(I)

Actual proof of the identity of the α-positions was obtained by Gilman and his students,[154] who showed that the same furoic acid was obtained by the two separate routes outlined below. By a similar procedure they likewise proved the identity of the β-positions. In this proof 2,5-dimethyl-3-furoic acid was proved to be identical to 2,5-dimethyl-4-furoic acid.



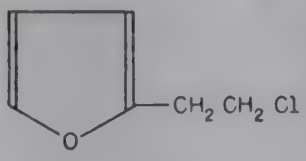
Four position-isomers are possible where furan is substituted twice by like substituents, the 2,3-, 2,4-, 2,5-, and 3,4-disubstitution products. Similarly it will be apparent that a disubstitution derivative possessing two unlike substituents can exist in six modifications; the methylfuroic acids comprise the only complete series of this type which has been described to date. Trisubstituted furans with like substituents exist in two isomeric forms; there can be only one tetrasubstituted furan where all substituents are alike. No further comment is required, since the number of isomeric polysubstitution products with dissimilar substituents can be deduced readily from the diolefin structure.

Nomenclature

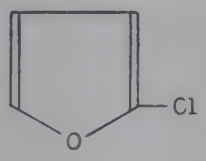
Furan is the name of the parent compound, rather than "furane," since the ending "ane" implies the absence of double bonds. Substituents are usually designated by number, for example, 2,4-dimethylfuran, 2-nitro-3-methylfuran. Greek letters may be used (e.g., α-bromofuran), but this method is generally restricted to monosubstituted furans.

[154] Gilman, Burtner and Vander Wal, *Rec. trav. chim.*, **52**, 151 (1933).

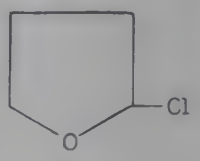
The radical with one hydrogen atom less than furan itself is named furyl. Where the substituent group is in the 2-position, no number designation is required, except to avoid ambiguity in those instances where a complex radical is attached to the ring [e.g., I may be named 2-(2-furyl)ethyl chloride, or β-2-furylethyl chloride]. Consequently, when no number designation is used, it will be understood that the substituent is in the 2-position of the compound (that is to say, the full name for furyl chloride, II, is



I



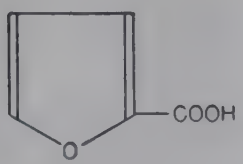
II



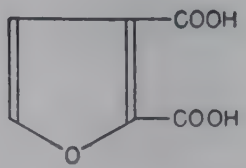
III

2-furyl chloride, α-chlorofuran, or 2-chlorofuran). Omission of the number in the furyl radical must, however, be restricted to the 2-isomer; the 3-isomer of II if named as a chloride, must be named 3-furyl chloride, or β-furyl chloride. The same general system is carried over to those derivatives in which the ring is saturated with hydrogen, except that the prefix "tetrahydro" is used. Thus, III is designated as 2-chlorotetrahydrofuran.

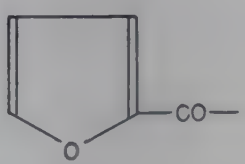
The carboxylic name for the acid, IV, is 2-furancarboxylic acid. Its common name is furoic acid; the early literature refers to it as pyromucic acid, because of its formation by pyrolysis of mucic acid. The isomeric acid is, therefore, called 3-furoic acid. A dicarboxylic acid such as V is named 2,3-furandicarboxylic acid. The acyl radical, VI, is designated furoyl, which is changed to 3-furoyl if the carbonyl group is attached to the 3-position. Furoyl corresponds to benzoyl and thenoyl for the benzene and thiophene analogs.



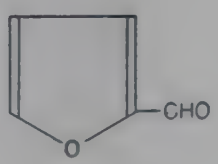
IV



V



VI

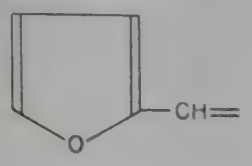


VII

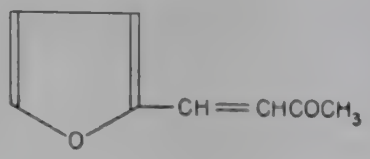
Aldehydes are ordinarily named by adding the ending "aldehyde" to the prefix of the name of the acid (e.g., benzoic acid, benzaldehyde). Thus, the aldehyde (VII) related to furoic acid would be named 2-furaldehyde, or simply furaldehyde. Its common name is furfural (furfur = bran), a non-systematic name, yet one so widely used that it would be unwise to make a change. In order to limit such departures from systematic nomenclature, however, it is strongly suggested that the prefix "furfur," where employed, be confined to 2-substituted furans. Names such as 5-methylfurfural and 4-isopropylfurfural conform to this plan, it being unnecessary to designate, by number, the position of the aldehyde group. In contradistinction, the isomeric compounds with the aldehyde group in the 3-position

should not be named as "furfurals" but as 3-furaldehydes (e.g., 5-methyl-3-furaldehyde, not 5-methyl-3-furfural).

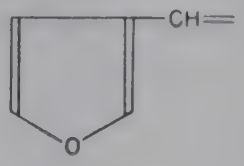
Furfurylidene is the name given to the bivalent radical VIII as in furfurylideneacetone, IX. It is regularly formed from furfuryl (cf. ethyl and ethylidene). Sometimes "furfural" is used for this radical, just as "benzal" is sometimes used for benzylidene. The corresponding radical, X, is called 3-furylmethylene.



VIII

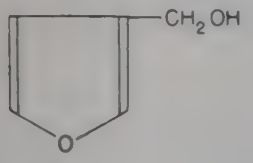


IX

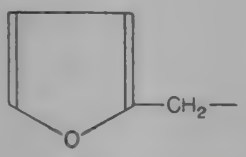


X

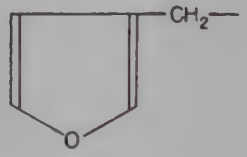
The alcohol obtained by reduction of the aldehyde group in furfural is known as furfuryl alcohol, the "furfur" syllable again implying attachment of the substituent at the 2-position. For the reasons outlined before, however, the isomeric alcohol, XI, is named 3-furylcarbinol or 3-furylmethanol, not 3-furfuryl alcohol. Radical XII is, therefore, called furfuryl (e.g., furfuryl acetate), but radical XIII must be named 3-furylmethyl as in 3-furylmethyl chloride, XIV.



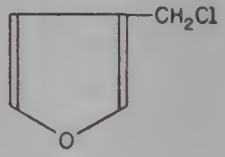
XI



XII



XIII



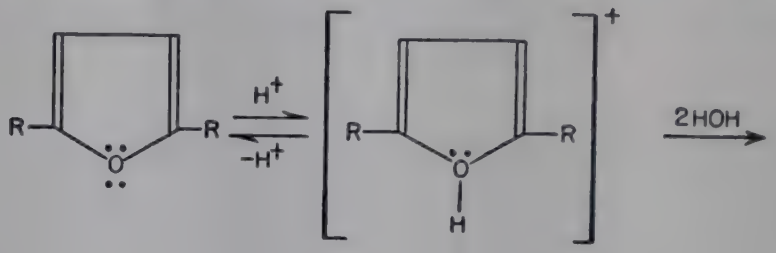
XIV

General Survey of Chemical Properties

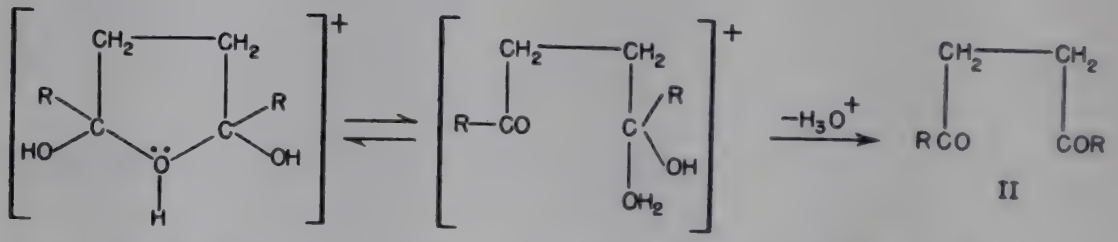
Previously it was stated that the furan ring should be looked upon as a cyclic, dienic ether, stabilized by resonance. In accordance with this view, furans should, and do, to a greater or lesser extent depending upon the nature of substituent groups, exhibit properties generally associated with vinyl ethers, conjugated dienes, and aromatic types. In fact, it is this ability to react in several directions, competitively, which is responsible for low product-yield in many reported reactions in the furan series. Examples of each type of behavior are cited throughout the monograph, and will not be repeated here. Rather, it seems desirable to attempt to generalize the polyfunctionality of the furan ring, and to discuss briefly some of the factors which affect the course of a given reaction, and the ease with which it goes forward.

Furan and its simple homologs are cleaved by aqueous acids. In this respect, they resemble the vinyl ethers although the furans are generally less susceptible to reaction on account of the relatively large resonance stabilization in the nucleus. Under acidic conditions, however, the resonance

energy may be largely dissipated. That is, coordination of the heteroatom with a proton, or other electron acceptor, would give rise to an ionic intermediate, I (where reagent is a proton acid), the oxygen atom of which can no longer enter into resonance with the other atoms in the ring.[b] The intermediate (I) would be considerably more reactive than its furan precursor, and would be expected to behave like a vinyl ether. In aqueous, acidic medium, the simple furans are converted into saturated 1,4-dicarbonyl compounds, II, a transformation which is in accord with this viewpoint, and which may proceed by addition of water to I as illustrated. Other



I



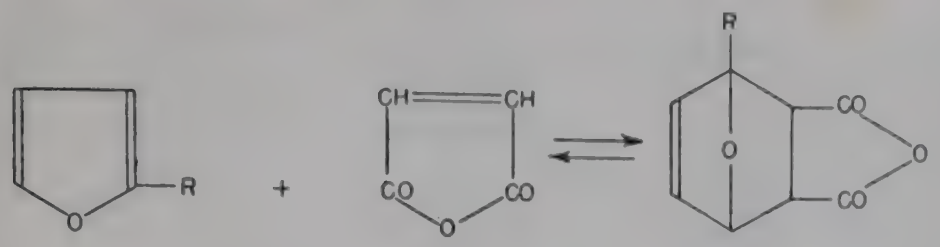
II

possible mechanisms are discussed elsewhere (Chapter 14), and in any event the reaction is usually accompanied by resinification, which may involve not only the starting furan compound but also the hydrolysis product. Of course, acid catalyzed resinification of the furans also goes forward in other than aqueous medium, indicating yet further the great reactivity of the intermediate ion.

The tendency for ionic types such as I to form is, obviously, a function of electron availability in the nucleus. Those furan derivatives possessing electron-withdrawing substituents (CHO, COOH, NO_2, etc.) are, therefore, more resistant to attack by acidic reagents than furan and its homologs. Additionally, certain substituent groups may offer competition to the nuclear oxygen atom as the initial point of attack by acids, and in some instances this competition may largely alter the course of reaction, as in the case of furfuryl alcohol (Chapter 14).

In common with olefinic types, the furans take part in a variety of addition reactions. For example, a number of Diels-Alder adducts (III) of the simple furans are known, indicating an electron-donor activity in the nu-

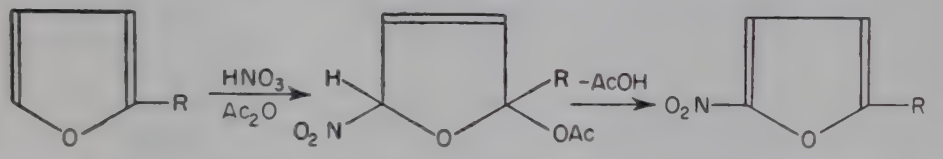
[b] It is considered unlikely that oxygen, an electronegative element, would donate more than one of its unshared electron pairs.



III

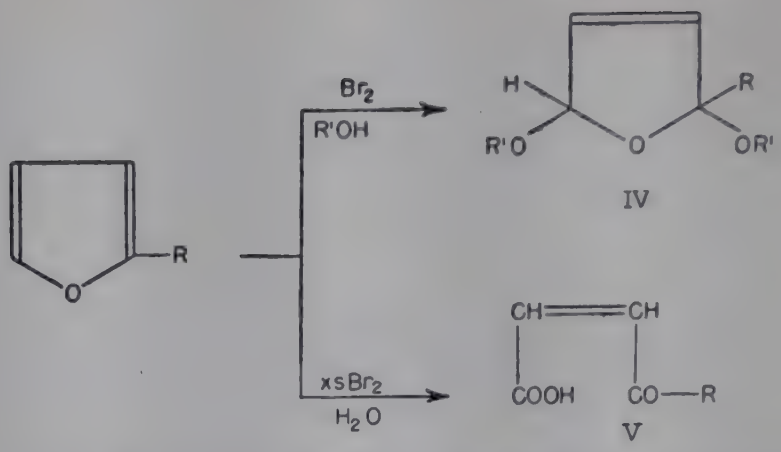
cleus similar to but, because of the high degree of resonance, less well developed than that exhibited by butadiene, cyclopentadiene and related compounds (Chapter 2). This dienic activity is further diminished by the introduction of electron-withdrawing substituents into the ring, so that furfural, for instance, fails to react with even strongly dienophilic compounds.

Halogens also add to the furan nucleus (Chapter 3), and intermediate addition compounds have been isolated in several experiments involving the nitration of furan compounds in acetic anhydride (Chapter 4). As in the case of III, these adducts appear to possess a 2,5-dihydrofuran configuration, and under favorable conditions, may revert to the more stable furan ring (the halogenation and nitration intermediates decompose to form



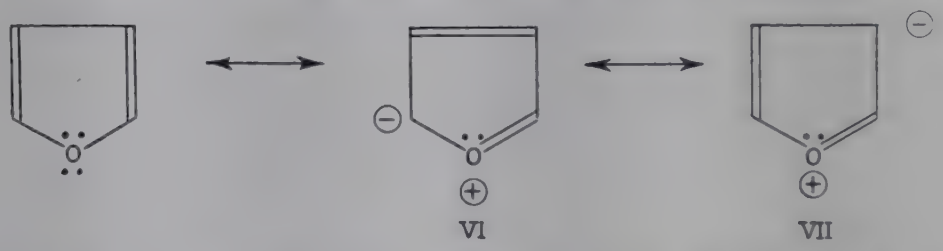
appropriately substituted furan compounds; III decomposes into its generators). In this respect, the furans behave in a manner intermediate in character between the truly dienic and truly aromatic types. That is, comparable dihydrobenzene types, if indeed they are formed at all, are incapable of isolation. The relative stability of these dihydrofuran compounds is, therefore, a mark of the inferior "aromaticity" of the furan ring compared with that of benzene. Also bearing on this point are the data available with reference to the simple furanols and furylamines. Unlike their benzene analogs (e.g., phenol and aniline), these furan types appear to exist largely in the tautomeric dihydro configuration; to behave in a manner somewhat related to aliphatic keto-enol and ketimine-eneamine systems, respectively (Chapter 5). In other words, the furan ring does not possess the integrity, as a unit, exhibited by the more aromatic ring systems.

The successful isolation of the substitution intermediates referred to above demands considerable care. Bromination in an inert medium (e.g., CS_2, $CHCl_3$), for example, has given rise to addition compounds in several reported instances. In alcohol, however, cyclic acetals (IV) may be obtained; in aqueous medium with excess bromine, maleic acid or related compounds (V) are generally formed (Chapters 2, 7, 9 and 12). Thus, the importance



of avoiding alcoholytic and hydrolytic conditions in attempted substitution reactions will be readily apparent, inasmuch as these conditions bring about oxidation, in the classical sense. The furan ring is also slowly attacked by oxygen on exposure to the atmosphere, the susceptibility being increased by the presence of acids and decreased by bases (Chapter 9). Hydrolysis of the autoxidized products gives rise to unsaturated γ-dicarbonyl compounds as before.

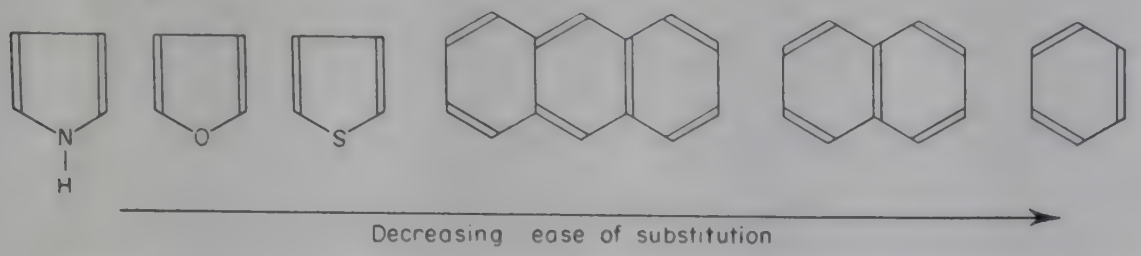
In the furan series, the common substitution reactions (nitration, sulfonation, halogenation, alkylation, acylation) show an almost exclusive α-orientation where such a position is available. Since all of these reactions involve attack on the ring by an electron-seeking group, this indicates that the resonance forms represented by VI are more important contributors to the hybrid molecule than those represented by VII. When both



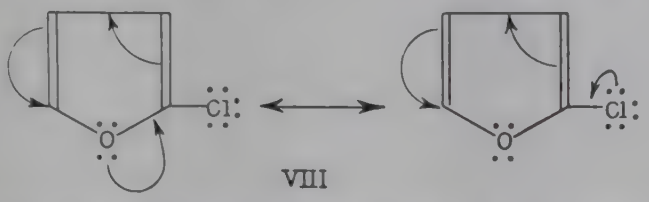
α-positions are occupied by irreplaceable groups, however, β-substitution can occur as is suggested by structure VII. The more facile substitution of furan types as compared to their benzene analogs is a natural consequence of the greater basicity, or electron-donor capacity, of the former. Evidence of this donor activity was previously brought out in discussing the participation of furan and its homologs as dienes in the Diels-Alder synthesis, a reaction which is not applicable in the benzene series. The relative donor tendencies are further illustrated by the preferential acylation of several furan types in benzene, and even in the more reactive toluene (Chapter 2), and also by the successful acylation of methyl furoate, whereas benzoic ester fails to acylate, at least under normal conditions (Chapter 12). Calloway[155]

[155] Calloway, *Chem. Revs.*, **17**, 327 (1935).

has suggested the following order of ease of substitution of various unsubstituted rings.

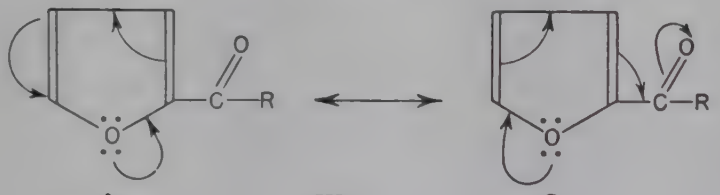


When an electron-releasing group is present in an α-position in furan, the selective α-orientation of an incoming substituent is facilitated by the fact that two electromeric effects are operating in the same direction (see 2-chlorofuran, VIII). On the other hand, an electron-withdrawing sub-



VIII

stituent in an α-position introduces an effect (IX B) which is in opposition to the ring effect (IX A). The tendency here is to stabilize the ring to



A IX B

attack by electron-seeking reagents, but the orientation effect is the same. That is, the reaction proceeds less readily, but results in α-substitution. Effect IX B, which creates a relatively electron-poor center in the nucleus, is revealed more distinctly in other circumstances: in reactions of negatively substituted furans with electron-donor or basic reagents. For example, 2-nitrofuran is completely destroyed by aqueous alkalies (Chapters 4 and 14), a reaction which again calls attention to the lesser integrity of the furan ring compared with that of benzene. Under somewhat similar conditions, nitrobenzene undergoes nucleophilic substitution with formation of *o*-nitrophenol. This difference in the behavior of these related types may be due to the fact that the postulated intermediate in the case of nitrofuran is, by virtue of the nuclear oxygen atom, an unsaturated, cyclic hemiacetal (Chapter 4), and would be expected to be quite unstable.

In addition to the general rule of α-orientation where possible, the following additional orienting influences have been put forward by Gilman and his students.[156, 157] In the case of di-α-substituted furans, the position

[156] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).
[157] Gilman, Calloway and Smith, *J. Am. Chem. Soc.*, **56**, 220 (1934).

taken by an incoming group is dependent upon the directive influences of the substituents already present. That is, if one of the latter is an ortho-para director in the benzene series, and the second is a meta-director, the entering group is directed to the β-position contiguous to the ortho-para director. Substitution of a β-substituted furan possessing two open α-positions follows these rules of orientation: (1) if the β-substituent is an ortho-para director, the incoming group enters the contiguous α-position; (2) if the β-substituent is a meta-director, the entering group goes to the more remote α-carbon atom.

In summary, it would appear that the furan ring exhibits a behavior pattern which is in agreement with the modern concept of its structural configuration, a resonance hybrid with several contributing forms. *A priori*, dienic and etheric properties were to be expected, since these two functions are combined in the nucleus. On the other hand, the reactivity of these functions is diminished by comparison with such types as butadiene and divinyl ether, respectively, to both of which furan bears some relationship. These lesser reactivities are a measure of the so-called aromatic character of the furan ring which, in turn, is less well developed than in the benzene series, as evidenced by the relative resonance energies of the two ring systems. Thus, furan compounds, as are other heterocyclic types, are representative of a sort of intermediate branch of organic chemistry. They may not be formally classified with either of the two main branches—the aliphatic and the aromatic compounds—but show resemblances to each. This complicating polyfunctionality presents, at once, a challenge and an opportunity to the investigator. The versatility of the furans suggests their potential value as sources of a wide variety of organic compounds. A great deal remains to be learned, however, with reference to operating conditions which will permit complete control of the direction of reaction and which will enable the experimenter to eliminate, or at least minimize undesired side-reactions. Nevertheless, a number of the reactions of furan types have already been developed to the point of industrial significance (Chapter 16), and the future should witness a great many more as this promising field of chemistry is further explored.

Chapter 2

FURAN AND ITS HOMOLOGS

Several of the compounds of this classification have been encountered in connection with studies of natural products. For example, furan itself and 2-methylfuran (sylvan) among others, have been found in wood oils, e.g., fir,[1] pine,[2, 3, 4] beech[5, 6] (see also [7, 8, 9, 10, 11]), and among the low-boiling carbonization products of cellulose,[12, 13, 14] sugars,[15, 16] and peat.[17] Furan has also been detected in the oil of roasted coffee.[18]

It may be added that the so-called carlina oxide derived from the root of *Carlina acaulis* is a furan compound, and has been assigned the structure of benzylfurylacetylene, I[19, 20] (see also [21, 22, 23]); perillene[a] from *Perilla frutescens* is reported to be 3-(4-methyl-3-pentenyl)furan, II[24, 25] (see

[a] Also referred to as perillon to avoid confusion with the hydrocarbon, perylene.

[1] Freundler, *Compt. rend.*, **124,** 1157 (1897).

[2] Atterberg, *Ber.*, **13,** 879 (1880).

[3] Fraps, *Am. Chem. J.*, **25,** 26 (1901).

[4] Aschan, *Z. angew. Chem.*, **20,** 1811 (1907).

[5] Harries, *Ber.*, **31,** 37 (1898).

[6] Jacquemain, *Bull. assoc. chim.*, **54,** 529 (1937).

[7] Pringsheim, *Z. angew. Chem.*, **40,** 1387 (1927); *C. A.*, **22,** 682 (1928).

[8] Pryanishnikov, Izpest'ev and Kropotov, *Trans. Inst. Pure Chem. Reagents U. S. S. R.*, **1939,** No. 16, 89; *Khim. Referat. Zhur.*, **1939,** No. 7, 129; *C. A.*, **34,** 4888 (1940); Russian Pat. 53,565 (1938); *C. A.*, **34,** 5276 (1940).

[9] Pryanishnikov and Grigorov, *Lesokhim. Prom.*, **1939,** No. 7, 12; *Khim. Referat. Zhur.*, **1939,** No. 12, 102; *C. A.*, **35,** 879 (1941).

[10] Pryanishnikov and Grigorov, *Lesokhim. Prom.* **3,** No. 3, 12 (1940); *C. A.*, **36,** 6331 (1942); Pryanishnikov, *Trans. Inst. Pure Chem. Reagents U. S. S. R.*, No. 17, 60 (1939); *Khim. Referat. Zhur.*, **1940,** No. 3, 91; *C. A.*, **36,** 2389 (1942); *Novosti Tekhniki* **9,** No. 3–4, 49 (1940); *C. A.*, **36,** 6780 (1942).

[11] Pryanishnikov, Russian Pat. 56,035 (1939); *C. A.*, **38,** 4779 (1944); Russian Pat. 58,132 (1940); *C. A.*, **38,** 5845 (1944).

[12] Sarasin, *Arch. sci. phys. et nat.*, **46,** 5 (1918).

[13] Fierz-David and Hannig, *Helv. Chim. Acta*, **8,** 900 (1925).

[14] Fierz-David, *Chemistry and Industry*, **44,** 942 (1925).

[15] Fischer and Laycock, *Ber.*, **22,** 101 (1889).

[16] von Lippmann, "Die Chemie der Zuckerarten," p. 301, Braunschweig (Brunswick) 1904.

[17] Christiansson, *Iva*, **18,** 89 (1947); *C. A.*, **42,** 5208 (1948).

[18] Johnston and Frey, *J. Am. Chem. Soc.*, **60,** 1624 (1938).

[19] Gilman, Van Ess and Burtner, *J. Am. Chem. Soc.*, **55,** 3461 (1933).

[20] Paul, *Compt. rend.*, **202,** 854 (1936).

[21] Semmler, *Ber.*, **39,** 726 (1906).

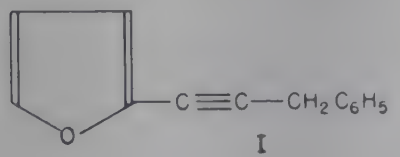
[22] Semmler and Ascher, *Ber.*, **42,** 2355 (1909).

[23] St. Pfau, Pictet, Plattner and Susz, *Helv. Chim. Acta*, **18,** 935 (1935).

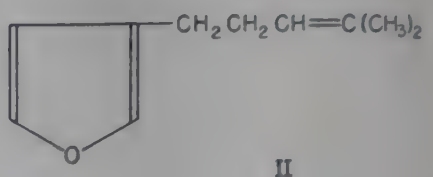
[24] Kondo and Suzuki, *Ber.*, **69,** 2459 (1936).

[25] Goto, *J. Pharm. Soc. Japan*, **57,** 77 (1937); *C. A.*, **31,** 4056 (1937).

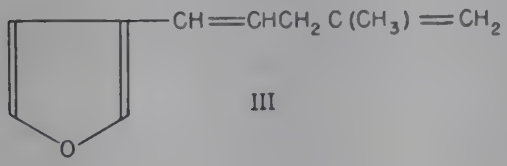
also [26, 27, 28]); α-clausenan from the oil of the leaves of *Clausena willdenovii* has been formulated as 3-(4-methyl-1,4-pentadienyl)furan, III.[29, 30, 31, 32] The compound $C_8H_{10}O_2$, named linderan because of its isolation from *Lindera strychinifolia vill*, is believed to be a dimer of 2,5-dihydrofuran or 3-(3-tetrahydrofuryl)furan, IV.[33]



I



II



III



IV

Preparation and Physical Properties

Furan

Furan was first prepared by dry distillation of barium furoate in admixture with soda lime[34, 35] (see also [36, 37]). In studying the other products of this decomposition, Freundler[1, 38] reported a small amount of di-2-furyl ketone,[b] and in the gaseous products he detected an unsaturated hydrocarbon which he believed to be cyclopropene. Unequivocal identification of the latter is still lacking, but in later work[40] the presence of the isomeric methylacetylene has been established. Additionally, Hurd and his stu-

[b] Reichstein[39] failed to find the ketone by this procedure (see also [40]).

[26] Kondo and Yamaguchi, *J. Pharm. Soc. Japan*, **446**, 263 (1919); *C. A.*, **13**, 1617 (1920).

[27] Suzuki, *J. Pharm. Soc. Japan*, **56**, 841 (1936); *C. A.*, **33**, 552 (1939).

[28] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta Phytochim.*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).

[29] Rao, *J. Sci. Ind. Research India*, **7**, No. 1, B, 11 (1948); *C. A.*, **42**, 5900 (1948).

[30] Rao and Subramaniam, *Proc. Indian Acad. Sci.*, **1**, A, 189 (1934); *C. A.*, **29**, 1209 (1935).

[31] Rao and Subramaniam, *Proc. Indian Acad. Sci.*, **2**, A, 574 (1935); *C. A.*, **30**, 2563 (1936).

[32] Rao and Subramaniam, *Proc. Indian Acad. Sci.*, **3**, A, 31 (1936); *C. A.*, **30**, 4494 (1936).

[33] Kondo and Sanada, *J. Pharm. Soc. Japan*, **526**, 1047 (1925); *C. A.*, **20**, 2678 (1926).

[34] Limpricht, *Ber.*, **3**, 90 (1870).

[35] Limpricht, *Ann.*, **165**, 253 (1873).

[36] Nasini and Carrara, *Gazz. chim. ital.*, **24**, I, 256 (1894).

[37] Hartley and Dobbie, *J. Chem. Soc.*, **73**, 598 (1898).

[38] Freundler, *Bull. soc. chim.* (3), **17**, 609, 613 (1897).

[39] Reichstein, *Helv. Chim. Acta*, **13**, 356 (1930).

[40] Hurd and Pilgrim, *J. Am. Chem. Soc.*, **55**, 1195 (1933).

dents[41] have shown that dry distillation of a mixture of sodium furoate and sodium hydroxide at 350–360° gives rise to furan in 93 per cent yield together with small percentages of carbon monoxide, hydrogen and acetylenic hydrocarbons.

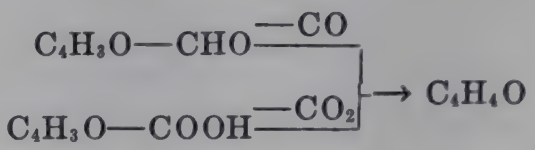
The most commonly employed laboratory procedure involves the pyrolysis of furoic acid in high-boiling crude tar base, and in the presence of a small amount of copper sulfate or copper oxide. Decarboxylation proceeds smoothly at temperatures in the range 170–220° to give furan in approximately 90 per cent yield[42] (see also [43, 44, 45]). Wagner and Simons[46] (see also [47, 48]) have described a similar procedure using the more expensive quinoline as the basic medium. They point out, however, that the quinoline and copper catalyst are recoverable, and can be used repeatedly without loss of efficiency.

In recent years, furan has become available on a commercial scale from furfural. The aldehyde and steam are passed over a mixed chromite of zinc and either manganese or iron at about 400°, and while few data are available on the operation, it is believed that the yield of furan is in excess of 90 per cent.[49, 50, 51] A similar decomposition of furfural into furan and carbon monoxide takes place when the aldehyde is passed over nickel or cobalt contact surfaces at 280°[52, 53] (see also [54, 55]). In these experiments it was observed that the inclusion of hydrogen with the input vapors (about two-thirds of a mole per mole of furfural) increased not only the yield of furan (up to 65 per cent) but also the effective life of the catalyst.[52] While most of the hydrogen is recovered unchanged, some hydrogenation occurs as evidenced by the formation of 2-methylfuran as a by-product. Other side-reaction products which were identified were *n*-butyraldehyde and propylene.

Furan is formed also (86 per cent yield) when vapors of furfural are led

[41] Hurd, Goldsby and Osborne, *J. Am. Chem. Soc.*, **54**, 2532 (1932).
[42] Gilman and Lousinian, *Rec. trav. chim.*, **52**, 156 (1933).
[43] Wilson, "Organic Syntheses," Collective Vol. 1, 2nd Ed., p. 274, New York, John Wiley and Sons, Inc. (1941).
[44] Sinkinson, *Ind. Eng. Chem.*, **17**, 27 (1925).
[45] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).
[46] Wagner and Simons, *J. Chem. Ed.*, **13**, 265 (1936).
[47] Heisig, *J. Am. Chem. Soc.*, **61**, 525 (1939).
[48] Cloke and Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).
[49] Whitman, (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,374,149 (1945); *C. A.*, **40**, 366 (1946).
[50] E. I. du Pont de Nemours and Co., Brit. Pat. 575,362 (1946); *C. A.*, **41**, 5551 (1947).
[51] Cass, *Chem. Ind.*, **60**, 612 (1947).
[52] Wilson, *J. Chem. Soc.*, **1945**, 61.
[53] Wilson and Imperial Chemical Industries Ltd., Brit. Pat. 553,175 (1943); *C. A.*, **38**, 4963 (1944).
[54] Padoa and Ponti, *Gazz. chim. ital.*, **37**, 105 (1907); *C. A.*, **2**, 1284 (1908).
[55] Codignola and Piacenza, Italian Pat. 421,627 (1947); *C. A.*, **43**, 5047 (1949).

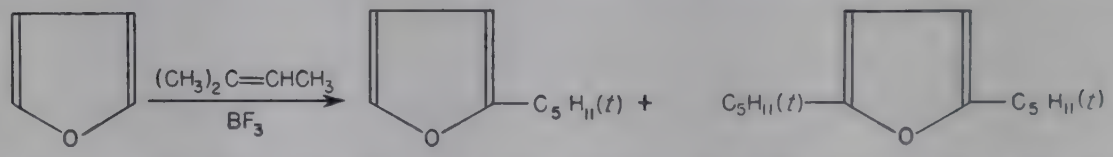
into an iron pipe containing soda lime at 350–360°[41] (see also [56]). A variation of this procedure using a contact bed of lime at about 480° and a mixture of furfural and steam has been patented by Cass and Cliver.[57] Non-catalytic pyrolysis of furfural likewise gives rise to some furan, but requires more rigorous temperature conditions. Thus, Hurd[41] obtained furan in 13–17 per cent yield on passing furfural through a quartz tube (5 seconds contact time) at 725°; the initial decomposition temperature was 565° for a contact time of twenty seconds.



For the transformation of pyrrole and thiophene into furan, see Yur'ev.[58] The latter is also reported as a product when acetylene, or formaldehyde, is conducted with steam over alumina at about 400°.[59] For its reported formation by cyclodehydration of succinaldehyde, see Harries[60] (see also [61]).

Alkyl- and Arylfurans

With only a few exceptions, the compounds of this classification (Table 2) have been prepared by indirect means. For example, until recently no direct alkylation of furan or its simple homologs had been successfully carried out (see Friedel-Crafts reaction, p. 64). However, Pines and Vesely[62] have lately described the synthesis of 2-*t*-pentyl- and 2,5-di-*t*-pentylfuran from furan and trimethylethylene under the influence of boron fluoride.



Similarly, the preparation of 2-arylfurans was accomplished by rather laborious routes prior to the work of Johnson,[63] who described the synthesis of several of these types by interaction of furan with aryldiazonium salts in the presence of alkali. In one experiment, using *p*-chlorobenzenediazonium acetate, Johnson made an interesting observation with regard to orientation and product distribution. That is, in addition to 2-*p*-chloro-

[56] Pringsheim and Noth, *Ber.*, **53**, 114 (1920).

[57] Cass and Cliver (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,337,027 (1943); *C. A.*, **38**, 3297 (1947).

[58] Yur'ev, *Ber.*, **69**, 1002 (1936).

[59] Chichibabin, *J. Russ. Phys.-Chem. Soc.*, **47**, 703 (1915); *Chem. Centr.*, **1916**, I, 920.

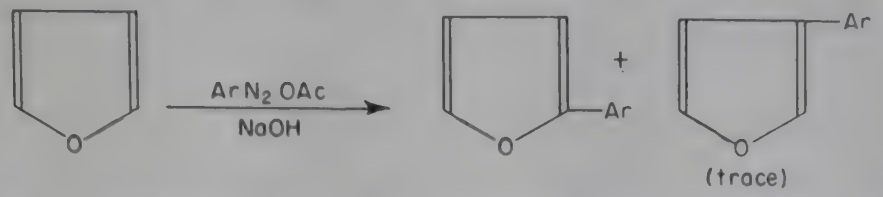
[60] Harries, *Ber.*, **34**, 1488 (1901).

[61] Metzner and Vorländer, *Ber.*, **31**, 1885 (1898).

[62] Pines and Vesely (to Universal Oil Products Co.), U. S. Pat. 2,532,515 (1950).

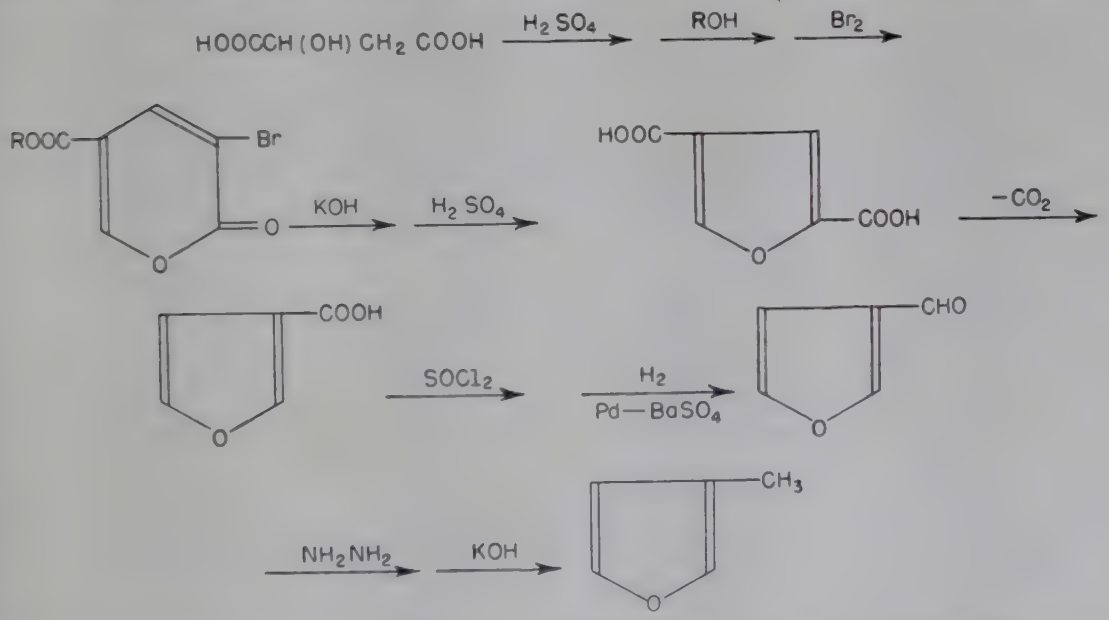
[63] Johnson, *J. Chem. Soc.*, **1946**, 895.

phenylfuran (29 per cent yield), he was able to isolate 3-*p*-chlorophenylfuran in 0.7 per cent yield, the first clear evidence of β-substitution of a furan



possessing an open α-position. The former product was also obtained (19 per cent yield) by condensing furan with *p*-chloronitrosoacetanilide.[63]

The paucity of mono-β-substituted alkyl- and arylfurans is attributable to the preferred α-substitution of furan types which complicates their synthesis. Other than 3-*p*-chlorophenylfuran (above), the known compounds of this class were obtained by indirect means, generally by ring closure reactions leading to a polysubstituted furan from which one or more substituents is subsequently removed. An example is the synthesis of 3-methylfuran by a tortuous route (below) involving, successively, the conversion of malic acid to coumalic acid, ester, 3-bromocoumalic ester, 2,4-furandicarboxylic acid,[64, 65] 3-furoic acid, 3-furoyl chloride, 3-furaldehyde and, finally, reduction to the desired product.[66, 66a] The route employed by Rinkes[67] (see also [68]) starting with diglycollic ester and chloroacetone, is equally circuitous, but represented the first synthesis of 3-meth-



ylfuran other than that previously achieved from the naturally occurring Elsholtzia ketone[28] which possesses a β-methyl substituent.

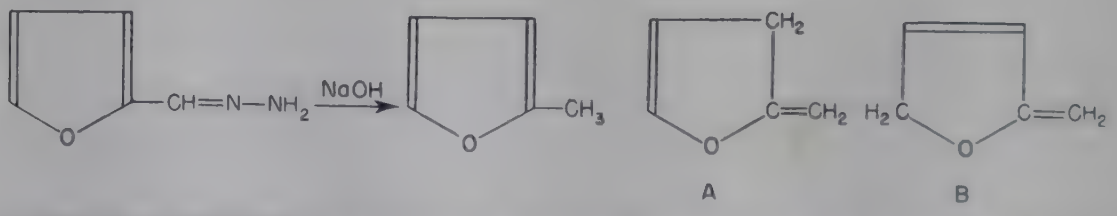
[64] Pechmann, *Ann.*, **264**, 261 (1891).
[65] Feist, *Ber.*, **34**, 1992 (1901).
[66] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 859 (1933).
[66a] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).
[67] Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931).
[68] Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).

The most important of the indirect methods of synthesis of furan homologs are summarized below. For convenience they are divided into two general categories depending upon whether or not the final step involves modification of a furan type.

Synthesis from Other Furans. *Decarboxylation of Appropriate Acids*

Just as furan may be derived from furoic acid (p. 31), so substituted furans are obtainable from appropriately substituted furoic acids. The ease of decarboxylation varies somewhat depending upon the location (α or β) of the carboxyl group(s) (see p. 493), but generally can be effected smoothly using a basic medium and a catalyst. The media which have been used most widely include quinoline and crude tar bases,[69] and β-naphthoquinoline.[70] Effective catalysts are copper-bronze[69] (see also [71]), copper chromite,[70, 72] copper sulfate and copper oxide,[42] and powdered copper[70] or nickel.[69] The technique is also applicable to furylalkanoic acids: 2-methylfuran from furylacetic acid[73]; 2-isopropylfuran from furylglutaric acid.[70] Accordingly, this method for the synthesis of alkyl- and arylfurans would appear to be limited only by the availability of appropriate carboxylic acids.

From Furan Aldehydes and Ketones. A number of the homologs of furan have been synthesized by catalytic hydrogenation of furan aldehydes and ketones (Chapter 15). They are also obtainable by Wolff-Kizhner reduction of these furan types (see, for example [74, 75, 76, 66a, 78]; pp. 384, 431). In the latter instance starting with furfural, 2-methylfuran is formed, but according to Kizhner[79] an unstable isomer (A or B) is produced simultaneously, the relative proportions varying with the rate of decomposition of furfural hydrazone. Very recently, Rice[80] has offered evidence in support of B as the accompanying product.



[69] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).
[70] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15**, 1118 (1932).
[71] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[72] Wilds and Johnson, *J. Am. Chem. Soc.*, **67**, 286 (1945).
[73] Runde, Scott and Johnson, *J. Am. Chem. Soc.*, **52**, 1284 (1930).
[74] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).
[75] Reichstein, Zschokke and Syz, *Helv. Chim. Acta*, **15**, 1112 (1932).
[76] Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 28 (1933).
[78] Alder and Schmidt, *Ber.*, **76**, 183 (1943).
[79] Kizhner, *J. Gen. Chem. U. S. S. R.*, **1**, 1212 (1931); *C. A.*, **26**, 5299 (1932).
[80] Rice, *J. Am. Chem. Soc.*, **74**, 3193 (1952).

From Furylcarbinols. Alkyl- and aralkylfurans have been obtained by reduction of the appropriate furylcarbinols using sodium and alcohol[81, 21, 22] (see also [82]), zinc dust in acetic acid,[83] and red phosphorus and iodine.[84] They have also been obtained by dehydration of the carbinols to the corresponding furylalkenes and subsequent catalytic hydrogenation (see Chapter 15).

Miscellaneous. An approach to mono-α-substituted homologs lies in the interaction of furfuryl bromide with the Grignard reagent.[85, 86]

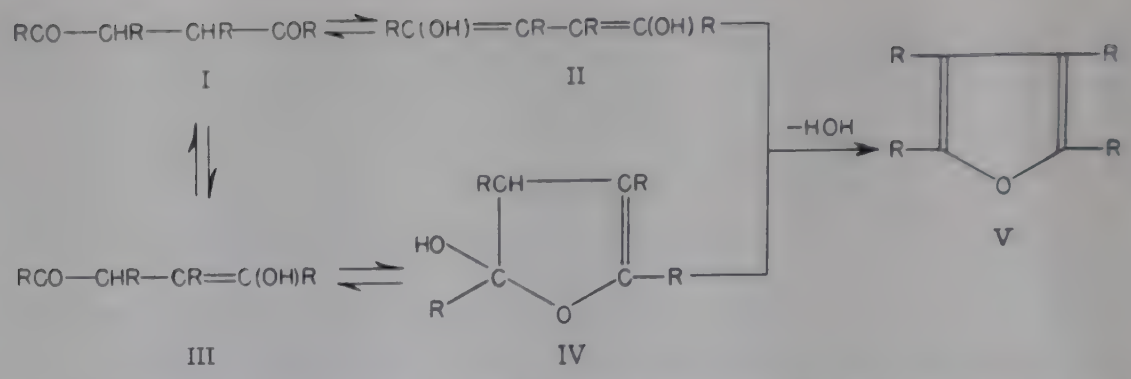
Other homologs have been prepared by removal of halogen from suitable halogenofurans (see Chapter 3).

Synthesis from Non-furan Types. Many of the compounds listed in Table 2, particularly the heavily substituted homologs, were obtained by cyclodehydration of saturated open-chain, 1,4-diketones. Ring closure of this type represents one of the oldest methods for the synthesis of furan compounds (see [87, 88, 89, 90, 91, 36]), and is apparently applicable to all diketones of the type indicated (I) with the exception of a few sterically hindered types, such as 1,4-bis(2,4,6-tri-*i*-propylphenyl)-1,4-butandione[92] (see also [93]). Catalysts for the reaction include sulfuric and hydrochloric acids, acetic anhydride, zinc chloride and phosphorus pentoxide, but recently Nowlin,[92] has reported superior results with polyphosphoric acid. Phosphorus pentahalides are also effective, but generally the dehydration reaction is accompanied by halogenation.[93a]

For the most part, the course of reaction has been more or less generally interpreted as proceeding by enolization of I and subsequent loss of the elements of water from the intermediate bisenol, II. Evidence given by Lutz and Reveley,[94] however, suggests that the enol, III, may be the key intermediate; that III cyclizes to the hemiacetal, IV,[c] which loses water to form the furan, V.

[c] Note that IV is identical with one of the intermediates postulated to explain the reverse reaction, hydrolytic cleavage of certain furan types to form saturated, 1,4-diketones (see p. 643).

[81] Paul, *Compt. rend.*, **202**, 1444 (1936).
[82] Birch, *J. Chem. Soc.*, **1945**, 809.
[83] Mahood and Aldrich, *J. Am. Chem. Soc.*, **52**, 4477 (1930).
[84] French and Smith, *J. Am. Chem. Soc.*, **67**, 1949 (1945).
[85] Paul, *Compt. rend.*, **200**, 1481 (1935).
[86] Woodward, *J. Am. Chem. Soc.*, **62**, 1478 (1940).
[87] Paal, *Ber.*, **17**, 2756 (1884).
[88] Dietrich and Paal, *Ber.*, **20**, 1077 (1887).
[89] Kapf and Paal, *Ber.*, **21**, 3053 (1888).
[90] Holleman, *Rec. trav. chim.*, **6**, 60 (1887).
[91] Magnanini and Angeli, *Ber.*, **22**, 853 (1889).
[92] Nowlin, *J. Am. Chem. Soc.*, **72**, 5754 (1950).
[93] Couper and Lutz, *J. Org. Chem.*, **7**, 79 (1942).
[93a] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 2145 (1934).
[94] Lutz and Reveley, *J. Am. Chem. Soc.*, **61**, 1854 (1939).

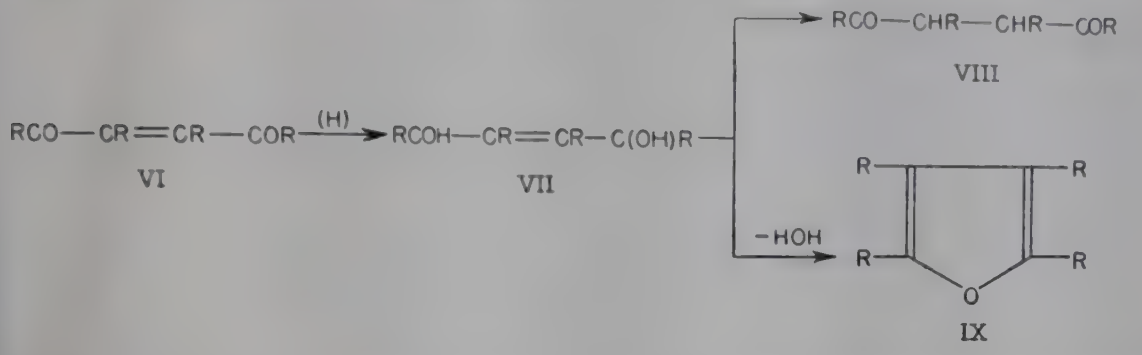


Under certain conditions, furans are also formed by reduction of unsaturated 1,4-diketones (see [95, 96, 97, 98]). For example, treatment of 1,2,3,4-tetraphenyl-2-buten-1,4-dione (dibenzoylstilbene), VI (R = C_6H_5), with zinc dust in acetic acid[d] gives rise to a mixture of the corresponding tetraphenylbutandione (VIII, R = C_6H_5) and tetraphenylfuran (IX, R = C_6H_5)[100] (see also [101, 102]). Lutz and his students[103, 104, 105, 94, 106, 107] applied this technique to related diketones; also reduction with stannous chloride,[108, 109, 110, 110a, 111, 93] and catalytically with hydrogen over platinum.[112, 94] In several instances, it was observed that furanization occurred under conditions which failed to produce a furan in appreciable quantity from the corresponding saturated diketone. Accordingly, Lutz[103, 113, 105, 112, 94] (see also [114]) concluded that the former reaction proceeds by 1,6-type addition of hydrogen to the conjugated enedione system of VI to form the dienol, VII; that VII may undergo either or both of two possible transformations, (a) rearrangement to the saturated diketone, VIII, and (b) de-

[d] In related reactions, Kohler and Tishler[99] report that the presence of zinc bromide exerts a pronounced catalytic effect on the formation of 2,3,5-triphenylfuran by reduction of 1,2,4-triphenyl-2-buten-1,4-dione (dibenzoylstyrene) using zinc and acetic acid.

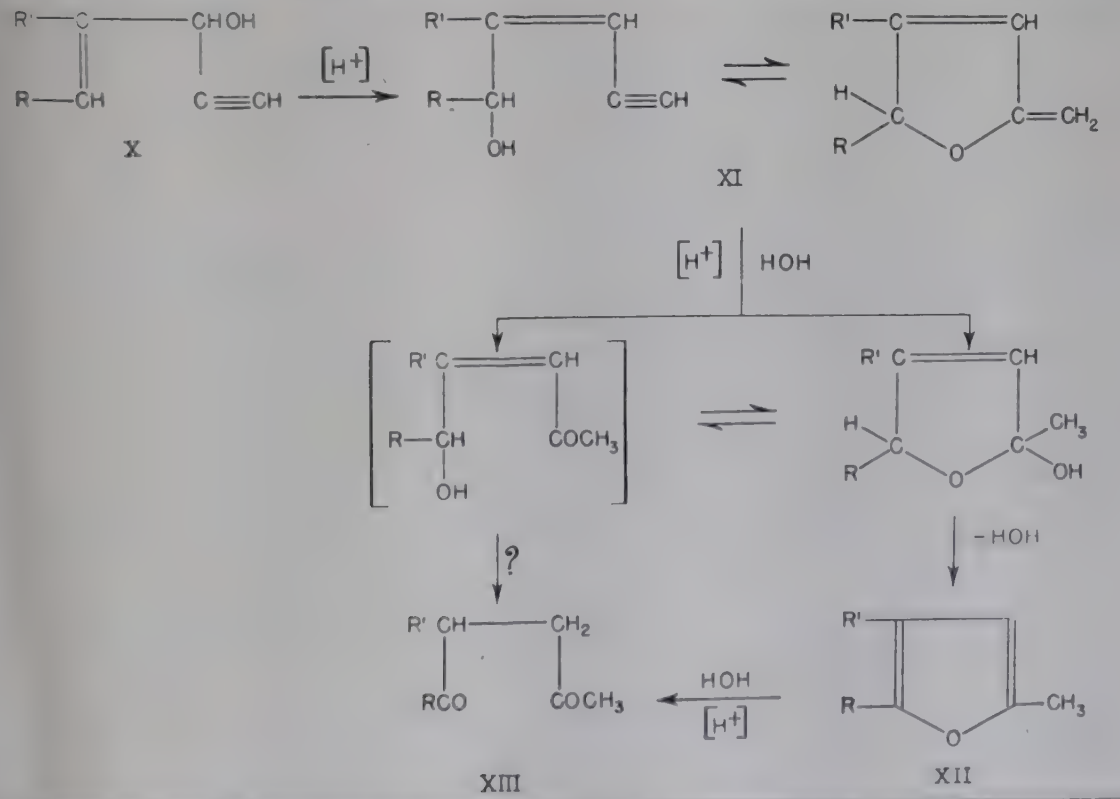
[95] Japp and Burton, *J. Chem. Soc.*, **51**, 430 (1887).
[96] Japp and Klingemann, *Ber.*, **21**, 2932 (1888).
[97] Japp and Klingemann, *J. Chem. Soc.*, **57**, 662 (1890).
[98] Japp and Maitland, *J. Chem. Soc.*, **85**, 1496 (1904).
[99] Kohler and Tishler, *J. Am. Chem. Soc.*, **57**, 217 (1935).
[100] Zinin, *J. prakt. Chem.*, **101**, 160 (1867).
[101] Dorn, *Ann.*, **153**, 349 (1870).
[102] Zinin, *Ber.*, **8**, 695, 1681 (1875).
[103] Lutz, *J. Am. Chem. Soc.*, **51**, 3008 (1929).
[104] Lutz and Taylor, *J. Am. Chem. Soc.*, **55**, 1593 (1933).
[105] Lutz, Love and Palmer, *J. Am. Chem. Soc.*, **57**, 1953 (1935).
[106] Lutz and Kibler, *J. Am. Chem. Soc.*, **61**, 3007 (1939).
[107] Lutz and Reveley, *J. Am. Chem. Soc.*, **63**, 3180 (1941).
[108] Lutz, Johnson and Wood, *J. Am. Chem. Soc.*, **60**, 716 (1938).
[109] Lutz and Boyer, *J. Am. Chem. Soc.*, **63**, 3189 (1941).
[110] Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2583 (1942).
[110a] Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2585 (1942).
[111] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70**, 1359 (1948).
[112] Lutz and Palmer, *J. Am. Chem. Soc.*, **57**, 1957 (1935).
[113] Lutz and Palmer, *J. Am. Chem. Soc.*, **57**, 1947 (1935).
[114] Conant and Lutz, *J. Am. Chem. Soc.*, **45**, 1047 (1923).

hydration to the furan, IX.[e] The relative yields of VIII and IX from VI depends upon operating conditions, including the nature of the solvent. (For related conversions of compounds of type VI to furanol derivatives, see Chapter 5; to halogen substituted furans, see Chapter 3). IX (R = C_6H_5)



has also been obtained, together with 1,2,3,4-tetraphenyl-1,4-butanedione, by the action of phenylmagnesium bromide on 1,2,4-triphenyl-2-buten-1,4-dione[115] (see also [94, 106]).

Substituted furans are also obtainable from vinylethynylcarbinols, X, derived by the action of acetylene on α,β-unsaturated aldehydes. These carbinols undergo rearrangement to XI when treated with acids, the latter giving rise to the furan, XII, when subjected to steam distillation in the presence of mercuric salts. Simultaneously, there is produced the saturated,

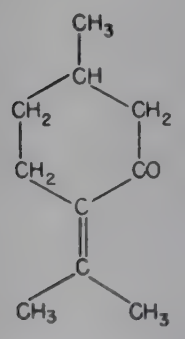


[e] The transformation of VII to IX probably does not take place directly, but rather by way of III and IV as indicated previously (see [94]).

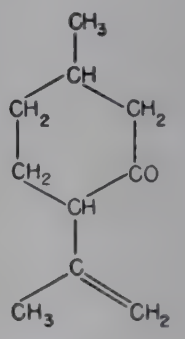
[115] Hahn and Murray, *J. Am. Chem. Soc.*, **36**, 1484 (1914).

1,4-diketone, XIII.[f] Thus, X (R = C_3H_7; R′ = C_2H_5) gives rise to 2-propyl-3-ethyl-5-methylfuran (25–60 per cent yield depending upon the experimental conditions) together with some 4-ethyl-2,5-octandione.[116, 117] 2,5-Dimethylfuran, which has been prepared in a similar manner from XI (R = CH_3; R′ = H),[118] is also formed as a by-product in the production of acetaldehyde from acetylene,[119] and by pyrolysis of acetone above 700°.[120] Related to the latter is the decomposition of acetophenone over alumina, which gives rise to a diphenylfuran, formulated as the 3,4-isomer by Ipat'ev and Petrov,[121] as the 2,4-isomer in the later work of Backer and Stevens.[122]

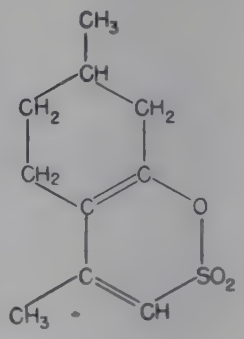
A relatively new synthesis for furans is an outgrowth of an investigation by Treibs[123, 124] concerning the action of a cold mixture of concentrated sulfuric acid and acetic anhydride on pulegone, XIV, and isopulegone, XV. Each gave rise to the same δ-sultone, XVI, which decomposed with loss of sulfur dioxide on application of heat with formation of **menthofuran,**[g] XVII. Morel and Verkade[126] later applied this procedure to other unsaturated



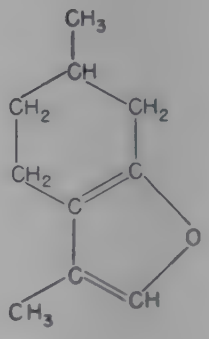
XIV



XV



XVI



XVII

ketones. For example, mesityl oxide, XVIII, was converted into the δ-sultone, XIX, which underwent pyrolysis to 2,4-dimethylfuran, XX. As yet,

[f] The diketone, XIII, is the product to be expected by hydrolytic cleavage of XII (p. 643). However, Heilbron[116] reports that its formation in this work must be explained, at least in part, by some other route.

[g] A constituent of many peppermint oils (see [125]).

[116] Heilbron, Jones, Smith and Weedon, *J. Chem. Soc.*, **1946**, 54.

[117] Heilbron, Jones and Sondheimer, *J. Chem. Soc.*, **1947**, 1586.

[118] Heilbron and Jones, Brit. Pat. 611,072 (1948); U. S. Pat. 2,470,070 (1949); *C. A.*, **43**, 4700, 5805 (1949).

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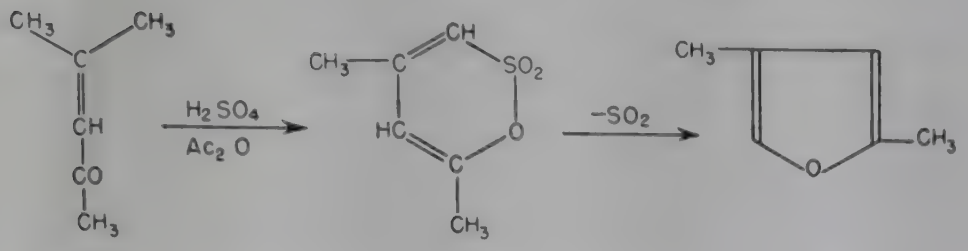
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[126] Morel and Verkade, *Rec. trav. chim.*, **67**, 539 (1948).



XVIII XIX XX

insufficient work has been carried out to permit comment on the limitations of the method; on the structural requirements of the starting ketones; on its possible application to unsaturated aldehydes. However, Morel and Verkade report success in the preparation of several furans possessing hydrocarbon radicals in the 2,4-, 2,3,4-, 2,3,5-, and 2,3,4,5-positions.

Properties

General

Furan is a colorless liquid of strong ethereal odor, possessing the physical properties listed in Table 1. It is only slightly soluble in water (*ca.* 1 per cent at 25°); miscible with alcohol, ether, acetone, ethyl acetate, petroleum ether and the aromatic hydrocarbons. Bremner and Keeys[127] report that it forms a constant boiling mixture (b.p. 30.5°) with water (1.2 per cent by weight). For the properties of furan and several of its derivatives as blending agents in fuels for internal combustion engines, see Nisbet,[128, 129] and Bayan and Beati.[130]

Table 1. Physical Properties of Furan

		Ref.
Boiling point	31.32–31.35°C. (760 mm.)	131,132
Specific gravity (d_4^{20})	0.9378, 0.9365, 0.9366	132, 133, 134, 135
Refractive index (n_D^{20})	1.4215	132, 133
Freezing point	−85.6°C.	136
Thermochemical data in calories/gram:		
Heat of formation (liquid)	217.7	45
Heat of combustion:		45
at constant volume	7354.4	
at constant pressure	7358.8	
Heat of vaporization (31.2°C.)	95.50	131
Specific heat (vapor):		137
at 44.33°C.	0.253	
at 67.71°C.	0.274	
at 98.99°C.	0.299	

[127] Bremner and Keeys, *J. Chem. Soc.*, **1947**, 1068.
[128] Nisbet, *J. Inst. Petrol.*, **27**, 293 (1941).
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[130] Bayan and Beati, *Chimica e industria Italy*, **23**, 432 (1941); *C. A.*, **36**, 7262 (1942).

The known alkyl- and arylfurans are listed in Table 2. Of these, only two, 2-methylfuran and 2,5-dimethylfuran, have received consideration as other than laboratory curiosities. The former, of course, is potentially available in commercial quantities by catalytic hydrogenation of furfural (Chapter 15); the latter has appeared in semi-commercial listings for several years. For the distillation characteristics of several binary and ternary systems containing 2-methylfuran the reader is referred to Holdren and Hixon,[138] and Pryanishnikov and Genin.[139]

TABLE 2. ALKYL- AND ARYLFURANS

Furan derivative	Physical constants (°C.)	Ref.
Monosubstituted		
2-Methyl	b.p. 62.8–63.5 (737 mm.) d_4^{20} 0.9132 n_D^{20} 1.4342, n_D^{18} 1.4339	73, 134, 79, 117, 140, 148, 138, 141, 142, 143; see also 144, 74, 146, 147, 82, 8, 139, 149, 150, 151, 152, 153
3-Methyl	b.p. 65–66 (atm.) d_4^{18} 0.923 n_D^{18} 1.4255	28, 68, 76, 67, 66a; see also 158
2-Ethyl	b.p. 92–93 (768 mm.) d_{15}^{13} 0.912 n_D^{13} 1.4466	140, 85, 74, 154, 155, 156, 157; see also 158
2-*n*-Propyl	b.p. 114.5–115.5 (750 mm.) d_4^{20} 0.8905, d_{25}^{25} 0.882 n_D^{20} 1.4459, n_D^{25} 1.4410	71, 159; see also 160
2-*i*-Propyl	b.p. 41.5 (65 mm.), 106–109 (atm.) d_{25}^{25} 0.8771 n_D^{25} 1.4466	71, 70, 161
3-*i*-Propyl	b.p. 111–112 (atm.) d_{20}^{20} 0.8929 n_D^{20} 1.4369	178
2-*n*-Butyl	b.p. 61 (49 mm.), 137–138 (atm.) d_{15}^{18} 0.889, d_{25}^{25} 0.8983 n_D^{18} 1.4464, n_D^{25} 1.4460	71, 140, 85; see also 162; p. 217
2-*i*-Butyl	b.p. 123–127 (atm.) d_{25}^{25} 0.886 n_D^{25} 1.4425	71
2-*sec*-Butyl	b.p. 132–135 (atm.)	71
2-*t*-Butyl	b.p. 119–120 (atm.) d_{25}^{25} 0.8708 n_D^{25} 1.4380	71, 163
2-*n*-Pentyl	b.p. 162 (atm.)	82; see also 164
2-*i*-Pentyl (?)	b.p. 169–171 (atm.) d_4^{20} 0.8996	162
2-*t*-Pentyl (?)	b.p. 59–60 (32.5 mm.) n_D^{20} 1.4459	62

TABLE 2—*Continued*

Furan derivative	Physical constants (°C.)	Ref.
2-*i*-Hexyl (?)	b.p. 76–78 (15 mm.) d_4^{20} 0.9014	162
3-*i*-Hexyl (dihydroperillene)	b.p. 181–182 (760 mm.) d_4^{22} 0.8852 n_D^{22} 1.4576	24, 25
2-(1,1-Di-*n*-propylbutyl)	b.p. 198–200 (atm.)	165
2-(1,1-Di-*i*-butyl-3-methylbutyl)	b.p. 208–210 (atm.)	165
2-(1,1-Di-*i*-pentyl-4-methylpentyl)	b.p. 98–100 (18 mm.)	165
2-Benzyl	b.p. 111.5–113.5 (16 mm.), 219 (754 mm.) d_{15}^{19} 1.050 n_D^{19} 1.5451, $n_D^{22.4}$ 1.5419	166, 85, 81
2-*o*-Hydroxybenzyl(*o*-furfurylphenol)	b.p. 151–153 (14 mm.) d_{15}^{17} 1.157 n_D^{17} 1.5689	167, 168
2-*p*-Methoxybenzyl	b.p. 144–145 (11 mm.) d_{16}^{10} 1.105 n_D^{10} 1.5509	169
2-(2-Hydroxy-5-methylbenzyl) (*o*-furfuryl-*p*-cresol)	b.p. 168–170 (15 mm.) d_{15}^{16} 1.143 n_D^{16} 1.5703	169
2-Phenethyl	b.p. 241–243 (760 mm.)	86; see also 170
2-(2-α-Piperidylethyl)	b.p. 245–247 (atm.) **hydrochloride,** m.p. 145–148	171
2-(2-*m*-Methoxyphenylethyl)	b.p. 153 (10 mm.)	86
2-(3-Phenylpropyl) (tetrahydrocarlina oxide)	b.p. 134–135 (10 mm.) d_4^{20} 1.007 n_D^{20} 1.5302	21, 22, 19, 23
2-Diphenylmethyl	m.p. 51	83
2-Phenyl	b.p. 92–95 (10 mm.), 107–108 (18 mm.) d_4^{20} 1.083 n_D^{20} 1.5920, 1.5968	172, 63; see also 173
2-*m*-Chlorophenyl	b.p. 137 (15 mm.) n_D^{25} 1.6053	63
2-*p*-Chlorophenyl	m.p. 70–71, 74–75	63; see also 174
3-*p*-Chloropheny	m.p. 50–51	63
2-*p*-Bromophenyl	m.p. 85–86	63
2-*p*-Aminophenyl	m.p. 53–54	63
2-*p*-Nitrophenyl	m.p. 134–135	63
2-α-Naphthyl	b.p. 90–91 (0.02 mm.) **picrate,** m.p. 105–106	63
2-(8a-Methyldecahydro-1-naphthyl)	b.p. 122–124 (0.4 mm.)	175
2-(10-Phenyl-9-anthryl)	m.p. 170	176

TABLE 2—*Continued*

Furan derivative	Physical constants (°C.)	Ref.
2-(3-Pyridyl)	b.p. 127–128 (25 mm.) **picrate,** m.p. 152 **methiodide,** m.p. 221–222 (dec.)	177
Disubstituted		
2,5-Isomers:		
2,5-Dimethyl	b.p. 92.8–93.3 (764.3 mm.) $d_4^{17.7}$ 0.9026, d_4^{20} 0.9000 n_D^{20} 1.4470	36, 116, 179; see also 88, 118, 180, 181, 120
2-Methyl-5-ethyl	b.p. 116–118 (742 mm.) d_4^{20} 0.8883 n_D^{20} 1.4473	159, 182
2-Methyl-5-*i*-propyl	b.p. 135–137 (770 mm.) d_4^{20} 0.8932 n_D^{23} 1.4429	183
2-Methyl-5-*sec*-butyl	b.p. 46 (13 mm.)	78
2-Methyl-5-pentyl	b.p. 88 (30 mm.) n_D^{17} 1.4548	116
2-Methyl-5-hexyl	b.p. 96 (20 mm.)	184
2,5-Di-*t*-pentyl (?)	b.p. 114.5 (31.5 mm.) n_D^{20} 1.4488	62
2-Methyl-5-phenyl	m.p. 41–42	185; see also 186, 87
2-Methyl-5-*p*-methoxyphenyl	m.p. 45.5–46	72
2,5-Diphenyl	b.p. 343–345 (atm.) m.p. 89.5–90, 91	187, 89, 188, 93, 189, 190, 111, 92; see also 191, 192, 193, 194
2-Phenyl-5-*p*-chlorophenyl	m.p. 123	195
2-Phenyl-5-*p*-bromophenyl	m.p. 127	196
2,5-Bis-*p*-chlorophenyl	m.p. 168–169	92
2,5-Bis-*p*-bromophenyl	m.p. 201–202, 206.5–208	197, 111, 92; see also 198
2,5-Bis-*o*-nitrophenyl (?)	m.p. 201	199
2,5-Di-*p*-tolyl	m.p. 165–166	90, 200, 92
2,5-Bis-(2,4-dimethylphenyl)	m.p. 95–96	200
2,5-Diveratryl	m.p. 154–155	201
2-Phenyl-5-mesityl	m.p. 30.5–31	109
2-*p*-Bromophenyl-5-mesityl	m.p. 84	109
2,5-Dimesityl	m.p. 82–83	108, 202, 193
2,5-Bisbromomesityl	m.p. 92–94	108, 193
2,3-Isomers:		
2,3-Dimethyl	b.p. 42 (115 mm.), *ca.* 87 (720 mm.)	76

TABLE 2—*Continued*

Furan derivative	Physical constants (°C.)	Ref.
2,4-Isomers:		
2,4-Dimethyl	b.p. 73 (720 mm.)	203, 204, 126
2-Methyl-4-phenyl	m.p. 80–81	205
2,4-Diphenyl	m.p. 111	172, 122; see also 206
3,4-Isomers:		
3,4-Dimethyl	b.p. 49 (125 mm.), 94 (720 mm.)	76
3,4-Diphenyl	m.p. 109–110.5	122, 121; see also 207
Trisubstituted		
2,3,4-Isomers:		
2,3,4-Trimethyl	b.p. *ca.* 54–55 (57 mm.)	75
2,3,4-Triphenyl	m.p. 137	208
2,3,5-Isomers:		
2,3,5-Trimethyl	b.p. 51.5 (62 mm.)	75
2-Propyl-3-ethyl-5-methyl	b.p. 64 (13 mm.) n_D^{18} 1.4562	116; see also 209
2,3-Dimethyl-5-phenyl	b.p. 100–115 (0.4 mm.)	210
3-Methyl-2,5-diphenyl	m.p. 57–58, 58–59	211, 110a, 212
3-Methyl-2,5-bis-*p*-bromophenyl	m.p. 158–159	110
3-Ethyl-2,5-diphenyl	b.p. 132–136 (0.1 mm.)	213
2,3-Diphenyl-5-*t*-butyl	m.p. 69–69.5 b.p. 196–199 (12 mm.)	98, 214
2-Diphenylmethyl-3-phenyl-5-trimethylphenyl	m.p. 128	99
3-*t*-Butyl-2,5-dimesityl	m.p. 132	107
2,3,5-Triphenyl	m.p. 92–93, 93–94	96, 97, 215, 216, 217; see also 95, 105, 112
2,3-Diphenyl-5-*p*-methoxyphenyl	m.p. 94–95	218
3-Phenyl-2,5-bis-*p*-bromophenyl	m.p. 114	219
2,3-Dicuminyl-5-phenyl	m.p. 85	220
2,3-Diphenyl-5-mesityl	m.p. 87	221
3-Mesityl-2,5-diphenyl	m.p. 157.5–158	106
3-Phenyl-2,5-dimesityl	m.p. 104–105.5	222
2,3,5-Trimesityl	m.p. 106.5	223
2,3-Diphenyl-5-*α*-naphthyl	m.p. 96	221
Tetrasubstituted		
Tetramethyl	b.p. 44 (12 mm.) m.p. *ca.* −30	75; see also 224
3,4-Dimethyl-2,5-diphenyl	m.p. 116–117	104, 93, 225; see also 226

TABLE 2—*Continued*

Furan derivative	Physical constants (°C.)	Ref.
3,4-Dimethyl-2,5-bis-*p*-bromophenyl	m.p. 181	93
3,4-Dimethyl-2,5-di-veratryl	m.p. 169–170	227
3,4-Dimethyl-2,5-di-mesityl	m.p. 144	104, 193
3,4-Dimethyl-2,5-bis-bromomesityl	m.p. 111.5-113	193
2,3,4-Triphenyl-5-benzyl	m.p. 163	228
2,3,4-Triphenyl-5-benz-hydryl	m.p. 183–184	84
Tetraphenyl (lepiden)	m.p. 174, 175	100, 91, 229, 230, 228, 231, 115, 232, 94, 233; see also 101, 234, 235, 102, 236, 237, 238
3,4-Bis-*p*-nitrophenyl-2,5-diphenyl	m.p. 211	239
Tetra-*p*-xenyl	m.p. 281–282.5	145

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Though relatively stable toward heat, furan decomposes at about 700° in a quartz tube; at 360° in contact (13–20 seconds) with a nickel catalyst. The pyrolysis products are carbon monoxide, gaseous hydrocarbons, and hydrogen. No difuryl is formed, indicating that the C—H bonds are more resistant to rupture than the C—O linkages[241] (see also [44]). In the hydrocarbon fraction[h] the following compounds were identified: acetylene, ethylene, propylene, and methane. Also present were methylacetylene, proven by its conversion to dipropynylmercury, $(CH_3C{\equiv}C)_2Hg$, and undetermined amounts of allene, cyclopropene and butadiene.[241] The last named product has been obtained in 16–20 per cent yield by passing vapors

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[h] Furan vapors are absorbed quantitatively by 82.5 per cent aqueous sulfuric acid, and it has been suggested that a mixture of furan and acetylene could be analyzed in this manner, since the latter is not absorbed unless fuming sulfuric acid is used.[242]

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[208] Quint, Pütter and Dilthey, *Ber.*, **71**, 356 (1938).
[209] Bowden and Jones, *J. Chem. Soc.*, **1946**, 52.
[210] Weidlich and Daniels, *Ber.*, **72**, 1590 (1939).
[211] Lauer and Spielman, *J. Am. Chem. Soc.*, **55**, 4923 (1933).
[212] Bailey and Lutz, *J. Am. Chem. Soc.*, **67**, 2232 (1945).
[213] Bailey and Hakki, *J. Am. Chem. Soc.*, **71**, 2886 (1949).
[214] Boon, *J. Chem. Soc.*, **97**, 1256 (1910).
[215] Smith, *J. Chem. Soc.*, **57**, 643 (1890).
[216] Japp and Michie, *J. Chem. Soc.*, **79**, 1010 (1901).
[217] Gilman and Melstrom, *J. Am. Chem. Soc.*, **68**, 103 (1946).
[218] Kohler and Allen, *J. Am. Chem. Soc.*, **50**, 884 (1928).
[219] Lutz, Tyson, Sanders and Fink, *J. Am. Chem. Soc.*, **56**, 2679 (1934).
[220] Smith, *Ber.*, **26**, 60 (1893).
[221] Smith, *Am. Chem. J.*, **22**, 249 (1899).
[222] Lutz and Kibler, *J. Am. Chem. Soc.*, **61**, 3010 (1939).
[223] Lutz and Kibler, *J. Am. Chem. Soc.*, **62**, 360 (1940).
[224] Willstätter and Clarke, *Ber.*, **47**, 291 (1914).
[225] Lutz and Bailey, *J. Am. Chem. Soc.*, **68**, 2002 (1946).
[226] Bailey and Nowlin, *J. Am. Chem. Soc.*, **71**, 732 (1949).
[227] Atkinson and Haworth, *J. Chem. Soc.*, **1938**, 1681.
[228] Pütter and Dilthey, *J. prakt. Chem.*, **149**, 183 (1937).
[229] Magnanini and Angeli, *Gazz. chim. ital.*, **19**, 270 (1889).
[230] Zalkind and Teterin, *J. prakt. Chem.*, **133**, 195 (1932).
[231] Dilthey and Kaffer, *Ber.*, **55**, 1275 (1922).
[232] Mitra, *J. Indian Chem. Soc.*, **15**, 59 (1938); *C. A.*, **32**, 4982 (1938).
[233] Dischendorfer, *Monatsh.*, **74**, 287 (1943); *C. A.*, **38**, 5822 (1944).
[234] Limpricht and Schwanert, *Ber.*, **4**, 335 (1871).
[235] Zinin, *Ber.*, **5**, 1105 (1872).
[236] Berlin, *Ann.*, **153**, 130 (1870).
[237] Bernhauer, Müller and Neiser, *J. prakt. Chem.*, **145**, 301 (1936).
[238] Barker, *J. Phys. Chem.*, **29**, 1345 (1925).
[239] Francis, *J. Chem. Soc.*, **111**, 1039 (1917).
[241] Hurd and Goldsby, *J. Am. Chem. Soc.*, **54**, 2530 (1932).
[242] Hurd and Goldsby, *J. Am. Chem. Soc.*, **54**, 2558 (1932).

of furan with hydrogen over a bed of activated carbon at about 425°[243] (see also [244]). For pyrolytic reactions of furan and its homologs leading to the formation of pyrroles and thiophenes, see p. 663.

It is probably true that most reactions of these furan types in the presence of acidic materials or acid-precursors (e.g., halogens), have given rise to some resin, the amount varying with the experimental conditions. While it has been possible, in several instances, to prepare saturated, aliphatic 1,4-diketones by the action of dilute, aqueous or alcoholic acids (p. 641), it is extremely difficult to entirely eliminate polymer formation. With concentrated hydrochloric[2] and hydrobromic acids,[245] resinification of 2-methylfuran proceeds with great vigor. The same is true when this furan is treated with dry hydrogen chloride, boron fluoride and the like; with hydrogen iodide, Nellensteyn [246] (see also [247]) reports a reaction leading to iodine, water and carbon. Concentrated hydrochloric acid rapidly discolors furan, finally producing a black, resinous material which Marcusson[248] found to contain chlorine. The very reactive acetyl iodide completely resinifies furan at room temperature with simultaneous precipitation of iodine.[249] As discussed later (p. 64), polymeric products are also formed by the action of the metal halides commonly employed to effect alkylation and acylation by the Friedel-Crafts procedure. For the copolymerization of furan with glycerides of highly unsaturated fatty acids under the influence of stannic chloride, see Ralston *et al.*[250]; with wood rosin in the presence of boron fluoride, see Rummelsburg.[251]

Unlike the more stable benzene ring, the furan heterocycle is very susceptible to oxidation. As a matter of fact, oxidation studies in the furan series are largely concerned with nuclear attack, it being difficult to find reagents and conditions which permit selective oxidation of a substituent group. A few of the exceptions are the oxidation of furfural (p. 388) and furyl methyl ketone (p. 431) to furoic acid, the conversion of furoin to furil (p. 483), the oxidation of 5-nitrofurfuryl alcohol to the corresponding aldehyde (p. 152) and of furfurylideneacetone to 3-(2-furyl)acrylic acid (p. 618). Ad-

[243] Yur'ev, Tronova, Kuznetsova, and Novosadova, *J. Gen. Chem. U. S. S. R.*, **17**, 131 (1947); *C. A.*, **42**, 164 (1948).

[244] Singleton (to Standard Oil Development Co.), U. S. Pat. 2,382,749 (1945); *C. A.*, **39**, 4886 (1945).

[245] Trefil'ev and Livanov, *J. Gen. Chem. U. S. S. R.*, **11**, 182 (1941); *C. A.*, **35**, 7960 (1941).

[246] Nellensteyn, *Chem. Weekblad.*, **24**, 102 (1927); *C. A.*, **21**, 2553 (1927).

[247] Morrell and Phillips, *J. Soc. Chem. Ind.*, **59**, 144 (1940); *C. A.*, **34**, 7629 (1940).

[248] Marcusson, *Mitt. Materielprüfungsamt.*, **40**, 245 (1922); *C. A.*, **17**, 2423 (1923); *J. Soc. Chem. Ind.*, **42**, 329A (1923).

[249] Stevens, *J. Am. Chem. Soc.*, **56**, 450 (1934).

[250] Ralston, McCorkle and Vander Wal (to Armour and Co.), U. S. Pat. 2,443,269 (1948); *C. A.*, **42**, 6580 (1948).

[251] Rummelsburg, U. S. Pat. 2,477,655 (1949); *C. A.*, **43**, 9486 (1949).

ditionally, there is the work of Brown[252] indicating the general usefulness of alkaline potassium ferricyanide for oxidizing furan methyl groups[i] to carboxyls. In this way, he was able to isolate some of the corresponding furancarboxylic acid from 2-methylfuran and furfuryl alcohol, among others.

$$C_4H_3O—CH_3 \xrightarrow{K_3Fe(CN)_6} C_4H_3O—COOH$$

Potassium permanganate is reduced by furan and its homologs. In this way 2-methylfuran may be degraded all the way to acetic acid[2], *sym*-difurylethane to succinic acid.[74] Interestingly enough, however, the related difurylmethane is reported to resist the action of alkaline permanganate; it also failed to react with ethyl nitrite and sodium ethoxide, when these reagents were used in an attempt to effect oxidation to difuryl ketoxime.[254]

Ozonization of furan gives rise to unstable, transparent, gelatinous products which are water-soluble and which are precipitable with *p*-nitrophenylhydrazine.[255] In one experiment, treatment of the resinous product with water permitted isolation of a highly colored compound, the analysis of which indicated the composition $C_{12}H_{12}O_{10}$. While no simple ozonide could be isolated, glyoxal was reported as a product of the partial ozonization of aqueous furan.[255]

On exposure to air or oxygen, furan and its homologs undergo autoxidation with formation of unstable, peroxidic products which resinify on standing. To stabilize furan against these changes, Cass[256, 257] recommends the addition of a small amount of hydroquinone; Copelin[258] employs pyridine as an inhibitor. The course of autoxidation has been the subject of considerable study by Schenck[259, 260, 261] (see also [261a]), who concluded that reaction goes forward in accordance with the general scheme illustrated below, leading to the formation of open-chain, unsaturated γ-dicarbonyl compounds, I[j]; that initiation is by way of a 1,4-type addition of oxygen to

[i] Furan methyl groups are reported to be oxidized to the aldehyde level by the action of nitrosyl chloride.[204]

[j] 3-Hexen-2,5-dione was obtained in approximately 50 per cent yield by autoxidation of 2,5-dimethylfuran.[260] For related transformation, see Schering, A.-G.[262]

[252] Brown, *Iowa State Coll. J. Sci.*, **11**, 227 (1937).

[254] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

[255] Freri, *Gazz. chim. ital.*, **63**, 281 (1933).

[256] Cass (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,489,265 (1949); *C. A.*, **44**, 1543 (1950).

[257] E. I. du Pont de Nemours and Co. and Cass, Brit. Pat. 619,645 (1949); *C. A.*, **43**, 5805 (1949).

[258] Copelin (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,436,764 (1948); *C. A.*, **42**, 3781 (1948).

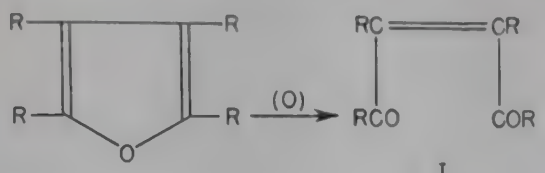
[259] Schenck, *Naturwissenschaften*, **31**, 387 (1943).

[260] Schenck, *Ber.*, **77**, 661 (1944).

[261] Schenck, *Chem. Ber.*, **80**, 289 (1947).

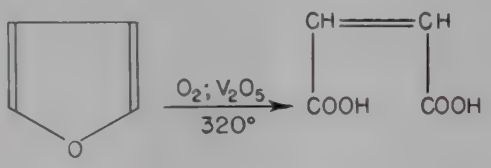
[261a] Schering, A.-G., French Pat. 883,593 (1943); *Chem. Centr.*, **1944, I**, 319.

the furan nucleus. With furan itself, an intermediate peroxide ($C_8H_8O_4$) was isolated by precipitation with petroleum ether, and this was converted



I

into succinaldehyde by catalytic hydrogenation. Similarly, hydrogenation of the peroxide derived from 2,5-dimethylfuran gave rise to acetonylacetone. Also included in Schenck's work were 2-methylfuran, 2-methyl-5-ethylfuran, 2,5-diphenylfuran, furoic ester, and several furylcarbinols and their ethers. Related is the formation of maleic acid when furan, in the vapor state, is passed with oxygen-containing gases over suitable catalysts at elevated temperature.[263, 264]



Oxidation of 2,5-diarylfurans by the action of mixed nitric and glacial acetic acids offers another synthetic approach to compounds of the general type I (above). The reaction, in essence a reversal of the preparation of furan types by reduction of α,β-unsaturated γ-diketones (p. 36), was first carried out by Zinin[100] (see also [97]), who obtained 1,2,3,4-tetraphenyl-2-buten-1,4-dione (I, R = C_6H_5) from tetraphenylfuran. It has since been employed extensively by Lutz and his students to other highly arylated furans. Almost invariably, the product is obtained in the *cis*-stereoisomeric configuration,[k] showing that the double bond is established prior to fission of the nuclear C—O linkage.[265] Consistent with this finding is the formulation of the reaction as a 1,4-addition of the reagent (nitric acid or its equivalent, anhydride or mixed anhydride) to the furan ring, and subsequent hydrolysis or acetolysis to the known product as outlined below.* Of the

* Compare nitration of furan (p. 142).

[k] In some instances the *cis*-form is unstable under the conditions of reaction and is subsequently rearranged to the *trans*-isomer.[265, 198] In general, however, the method may be employed for the preparation of *cis*-unsaturated diketones which are difficultly accessible by other routes.[193, 110a] A related type of oxidation was noted on refluxing 2,5-diphenyl-3,4-dichlorofuran with phosphorus pentachloride. Subsequent hydrolysis of the reaction mixture gave rise to 1,4-diphenyl-2,3-dichloro-2-buten-1,4-dione in 80–90 per cent yield.[93a]

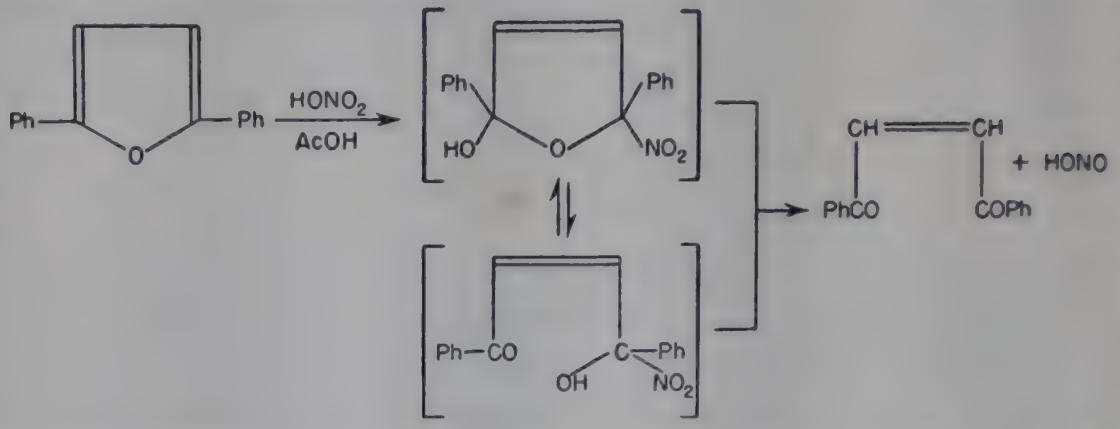
[262] Schering, A.-G., Belgian Pat. 446,142 (1942); *C. A.*, **39**, 1106 (1945).

[263] Milas and Walsh, *J. Am. Chem. Soc.*, **57**, 1389 (1935).

[264] Milas and Walsh (to Research Corp.), U. S. Pat. 2,118,567 (1938); *C. A.*, **32**, 5409 (1938).

[265] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 978 (1934).

many 2,5-diarylfurans so treated,[93a, 266, 219, 267, 106, 268, 110, 110a, 269, 218] only



the 2,5-dimesityl types resisted oxidative cleavage. This result is not inconsistent with the postulated mechanism, inasmuch as the bulky mesityl groups would be expected to hinder the intermediate addition reaction.[193] However, when Lutz and Boyer[109] observed that the reaction goes forward with ease when one of the α-carbon atoms of the furan nucleus is free from excessive steric hindrance (unsymmetrical 2,5-diarylfurans carrying only one mesityl group are oxidized by the mixture of nitric and acetic acids), they considered this finding to refute the above mechanism on the basis that hindrance at one end of the diene system of the furan ring should be practically as effective as hindrance at both ends. Clauson-Kaas[270] has questioned the soundness of this argument on the basis that it is valid only if both of the radicals involved in the intermediate addition step are identical, which is not the case in nitric acid oxidation.

There is a great deal of additional evidence indicating that the reaction of furan types with oxidizing agents is largely initiated by 1,4-type additions[1] of the reagent to the nucleus (see also pp. 219, 385, 494). Thus, 2,5-diacetoxy-2,5-dihydrofuran, II, is obtained in 45 per cent yield by treating furan with lead tetracetate in acetic acid[270] (see also [272]); in 70 per cent yield by the action of bromine on furan in acetic acid containing potassium acetate.[272a] The structure of II was proven by subsequent hydrolysis to malealdehyde, III, and acetic acid[270] (see also [272]). Oxidation with hydrogen

[1] Though somewhat inconclusive, Boeseken's[271] study of the action of peracetic acid on furan types would indicate that, to a certain extent, some 1,2- attack occurs (see also p. 394).

[266] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 1193 (1934).

[267] Lutz and Stuart, *J. Am. Chem. Soc.*, **59**, 2316 (1937).

[268] Lutz and Smith, *J. Am. Chem. Soc.*, **63**, 1148 (1941).

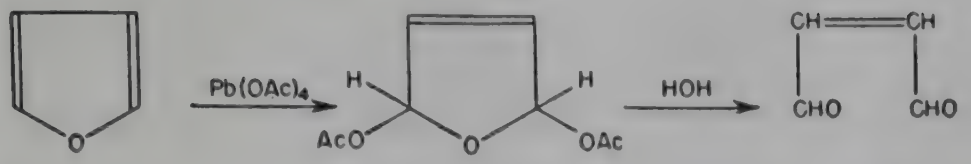
[269] Lutz and Bailey, *J. Am. Chem. Soc.*, **67**, 2229 (1945).

[270] Clauson-Kaas, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd*, **24**, No. 6, 18 pp. (1947); *C. A.*, **42**, 1930 (1948).

[271] Boeseken, Vermij, Bunge and Van Meeuwen, *Rec. trav. chim.*, **50**, 1023 (1931).

[272] Clauson-Kaas, *Acta Chem. Scand.*, **1**, 397 (1947).

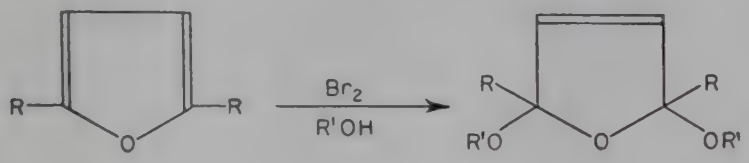
[272a] Clauson-Kaas (to Kemisk Vaerk Koge A/S), U. S. Pat. 2,514,026 (1950); *C. A.*, **44**, 8375 (1950).



II III

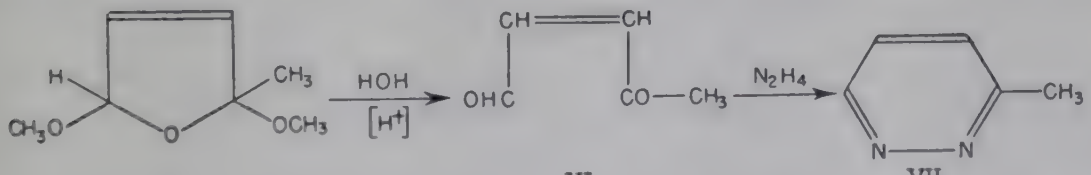
peroxide in aqueous methanol in the presence of osmium tetroxide likewise results in the formation of III, but a portion of the latter is hydroxylated yet further to give *meso*-tartaraldehyde as a companion product.[273] Again, Clauson-Kaas[274] obtained III (in 23 per cent yield as the bisphenylhydrazone) by the action of perbenzoic acid on furan in chloroform (see also [271]).

Related to II are the 2,5-dialkoxy-2,5-dihydrofurans, IV, derived from furan and its homologs by careful oxidation with bromine[272, 274, 275, 276, 277, 277a] or chlorine[278, 279] in the appropriate alcohol, and in the presence of a substance capable of neutralizing the liberated hydrogen halide (for example, potassium acetate, sodium carbonate, etc.). As cyclic acetals of



IV

malealdehyde and its homologs, the compounds of type IV are readily hydrolyzed to the appropriate 1,4-dicarbonyl compound. Thus, 2-methyl-2,5-dimethoxy-2,5-dihydrofuran, V, obtained by methoxylation of 2-methylfuran with methanolic bromine, is readily cleaved to 3-acetylacrolein, VI. The structure of VI, and therefore of V, was established by synthesis of the known 3-methylpyridazine, VII, by the action of hydrazine on the hydrolysis product, VI.[275] Attempted nuclear acetoxylation of 2-methylfuran with bromine in acetic acid containing potassium acetate failed.



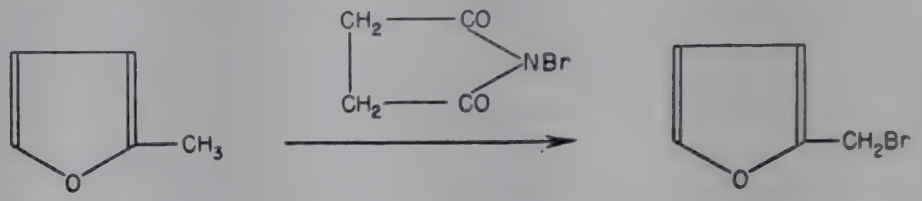
V VI VII

Distillation (1 mm.) of the reaction mixture brought about rapid decom-

[273] Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, **1**, 216 (1947).
[274] Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, **1**, 415 (1947).
[275] Clauson-Kaas and Limborg, *Acta Chem. Scand.*, **1**, 619 (1947).
[276] Clauson-Kaas, Limborg and Fakstorp, *Acta Chem. Scand.*, **2**, 109 (1948).
[277] Fakstorp, Raleigh and Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950).
[277a] Clauson-Kaas, Li and Elming, *Acta Chem. Scand.*, **4**, 1233 (1950).
[278] Jones (to Imperial Chemical Industries Ltd.), Brit. Pat. 595,041 (1947); *C. A.*, **42**, 2992 (1948).
[279] Jones (to Imperial Chemical Industries Ltd.), U. S. Pat. 2,475,097 (1949); *C. A.*, **43**, 7970 (1949)

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position which was attributed to the formation of furfuryl bromide.[276] That the bromide may have been formed was indicated by the isolation of a small quantity of furfuryl acetate. Lateral bromination had previously been achieved by the Wohl-Ziegler technique which permits selective bromination of a furan alkyl substituent. Thus, N-bromosuccinimide reacts vigorously with 2-methylfuran to form furfuryl bromide; with 2,5-dimethylfuran to give 5-methylfurfuryl bromide.[280]



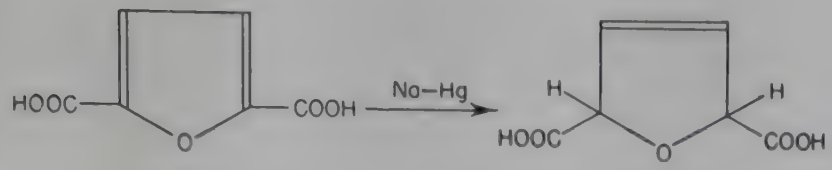
Reducing agents such as dissolving metals, electrolytic cathodes, sodium, and the like do not, as a rule, attack the furan ring. For example, sodium amalgam is without action on furan[35]; zinc, sodium amalgam and various cathodes fail to effect reduction of 2-methyl-5-ethylfuran[182] or 2-methyl-5-phenylfuran.[186] These reagents readily reduce carbonyl groups, and ethylenic bonds conjugated with such groups, hence it is not surprising that they attack furfural (p. 383), furfurylideneacetone (p. 466), and related types, but even in these instances reduction is confined to the side chain. Thus, furfurylideneacetophenone, VIII, is converted into 1-phenyl-3-(2-furyl)-propyl alcohol, IX, by the action of sodium amalgam.[22] The same product, together with 2-(3-phenylpropyl)furan, X, was obtained when the reduction was carried out with sodium and alcohol.[22, 21] Under the latter conditions, phenylfurylcarbinol is similarly reduced to 2-benzylfuran.[81] 2-Furoic acid

$$\underset{\text{VIII}}{C_4H_3O{-}CH{=}CHCOC_6H_5} \xrightarrow[EtOH]{Na} C_4H_3O{-}CH_2CH_2CH(OH)C_6H_5 + C_4H_3O{-}CH_2CH_2CH_2C_6H_5$$

IX X

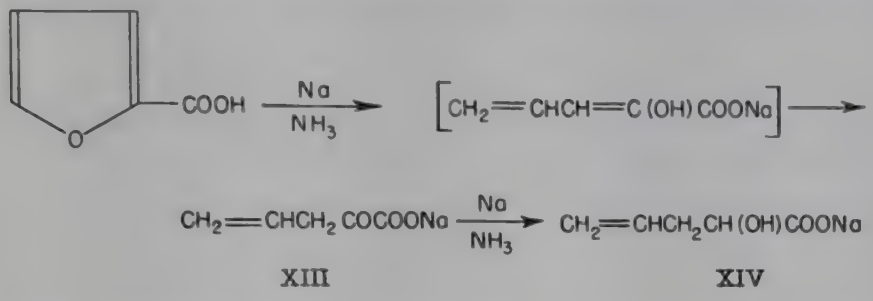
is unaffected by these reagents,[281] (p. 497), although the open-chain analog, β-vinylacrylic acid takes up two atoms of hydrogen quite readily under similar conditions.[282] On the other hand, when the ring carries two carboxyl groups, reduction proceeds easily under the influence of sodium amalgam. Thus, 2,5-furandicarboxylic acid, XI, gives rise to the *cis*-2,5-dihydro compound, XII, which slowly isomerizes to the *trans*-acid,[283, 284] (p. 574). While sodium in liquid ammonia had no effect on 2-methylfuran or furfuryl

[280] Buu-Hoi and Lecocq, *Compt. rend.*, **222**, 1441 (1946).
[281] Yoder and Tollens, *Ber.*, **34**, 3447 (1901).
[282] Isaacs and Wilson, *J. Chem. Soc.*, **1936**, 810.
[283] Hill and Wheeler, *Am. Chem. J.*, **25**, 463 (1901).
[284] Cypher, M. S. Thesis, University of Notre Dame, 1948.



XI XII

alcohol, a reductive cleavage was observed with 2-furoic acid, which gave rise to sodium 2-oxo-4-pentenoate, XIII, subsequently reduced further to the hydroxy acid, XIV.[285] Non-catalytic reduction of highly phenylated



XIII XIV

furans has been reported in two instances. 2,5-Diphenyl-,[286, 287] and 2,3,5-triphenylfuran[97] have been reduced with sodium and alcohol to tetrahydro compounds, and even to more highly hydrogenated derivatives of unknown constitution.

In summary, the common reducing agents are without effect on the furan ring except in a few experiments wherein it is substituted by carboxyl or phenyl groups. However, the nucleus can be reduced readily using hydrogen in the presence of a suitable catalyst (Chapter 15). In this way, four atoms of hydrogen can be added to the ring to form the appropriate tetrahydrofuran compounds, or the nucleus may undergo hydrogenolysis of a C—O linkage leading to straight chain compounds.

Addition reactions are, of course, not confined to hydrogen. Furan types also combine additively with chlorine and bromine under suitable conditions (Chapter 3). In this connection, it has been reported that "pyridine-sulfate-bromide" reagent[m] effects complete saturation of the ring in furan, methylfuran and furfuryl alcohol with little, if any, substitution. This behavior has been made the basis for the analytical determination of these types.[288] Addition compounds have also been obtained, as intermediate products, in nitration reactions using a mixture of nitric acid and acetic anhydride as the nitrating agent (Chapter 4). The interaction of methyl-

[m] This reagent (0.05*N* with respect to bromine) is prepared by dissolving pyridine, sulfuric acid, and bromine in glacial acetic acid. Certain furan compounds, e.g., furfural and furoic acid, are unaffected by the reagent, so that it is possible to estimate furan and its homologs in the presence of these types.[288]

[285] Rosenblum and Wilson, unpublished.

[286] Kapf and Paal, *Ber.*, **21**, 3057 (1888).

[287] Perkin and Schloesser, *J. Chem. Soc.*, **57**, 955 (1890).

[288] Angell, *The Analyst*, **72**, 178 (1947).

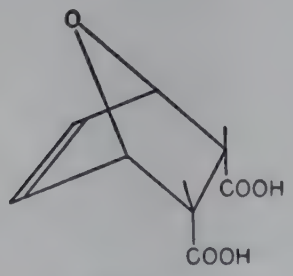
magnesium iodide and 2,5-dimethylfuran gives rise to a coordination compound which separates by precipitation; no evidence of Grignard-exchange was observed.[289] A clathrate type compound, formulated as $C_4H_4O \cdot NH_3 \cdot NI(CN)_2$,[290] is formed by combination of furan with ammonia-nickel cyanide complex.[291] For other manifestations of the tendency of furans to form addition compounds, see [292]; see previous discussion of oxidation reactions; see behavior of furans in the diene synthesis.

Diene Synthesis with Furan Compounds

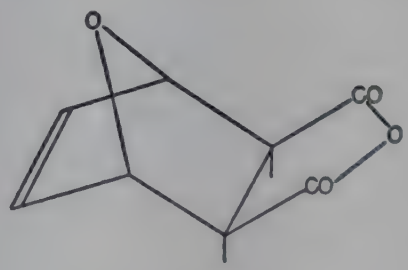
The 1,4-conjugate system of the nucleus in furan and its homologs is sufficiently dienic in character to permit ready participation in the Diels-Alder reaction with maleic anhydride, and several other dienophilic substances. A review of much of the published work with furan compounds is to be found in Norton's excellent summary of the Diels-Alder diene synthesis.[293]

Addition is sterically selective, with formation of cyclic adducts possessing the *endo* configuration.[n] [297] Thus furan and its homologs react with

[n] In a recent paper, Woodward and Baer[294] demonstrate that in the reaction of furan with maleic derivatives both stereochemical adducts may be formed, depending upon reaction conditions and the nature of the addend. Thus, furan and aqueous maleic acid give adduct (A) whereas furan and maleic anhydride in ether react with the formation of the alternate *cis* adduct (B).



(A)



(B)

In the earlier work of Diels, Alder and co-workers,[295, 296, 297] it was assumed that the acid obtained by hydrolysis of the crystalline anhydride (II) was identical to I. However, I could not be isolated from its solutions apparently due to facile dissociation into its generators. On the other hand, the acid obtained from II may be purified by recrystallization from warm water.

[289] Hurd and Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

[290] Hofmann and Arnoldi, *Ber.*, **39**, 339 (1906).

[291] Powell and Rayner, *Nature*, **163**, 566 (1949).

[292] Gilman, Wooley and Vander Wal, *Proc. Iowa Acad. Sci.*, **39**, 176 (1932); *C. A.*, **28**, 6714 (1934).

[293] Norton, *Chem. Revs.*, **31**, 319 (1942).

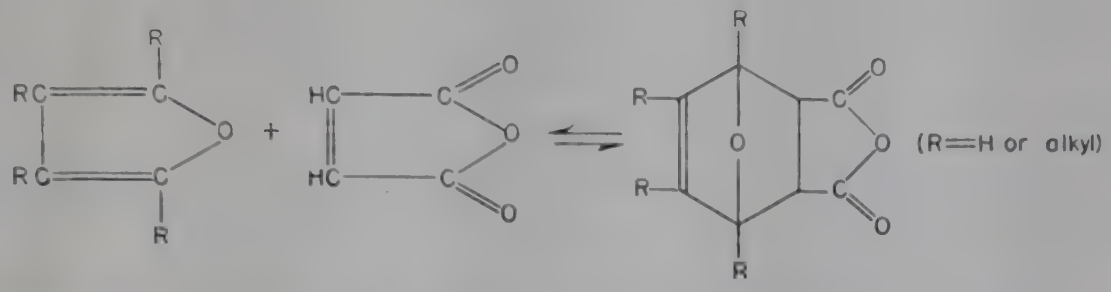
[294] Woodward and Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

[295] Diels, Alder and Naujoks, *Ber.*, **62**, 554 (1929).

[296] Diels, Alder, Nienburg and Schmalbeck, *Ann.*, **490**, 243 (1931).

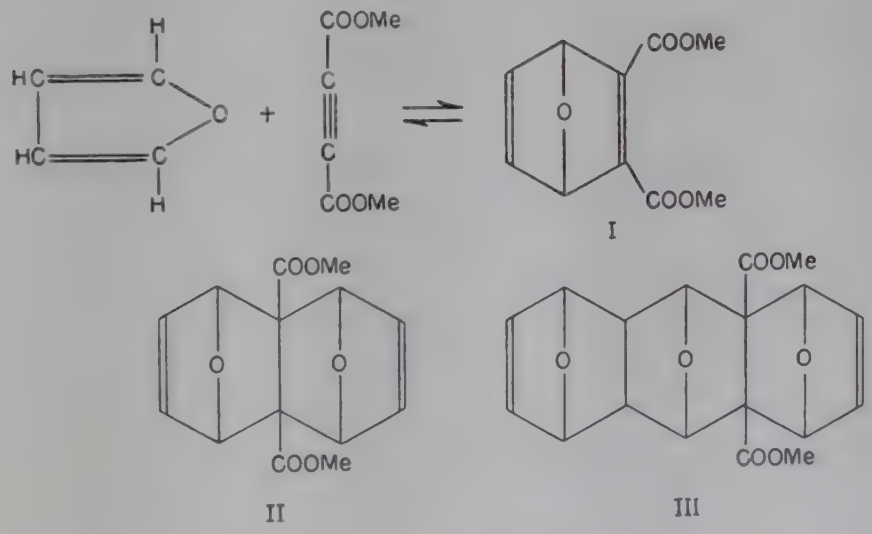
[297] Alder and Backendorf, *Ann.*, **535**, 101 (1938).

maleic anhydride to give 3,6-oxy-1,2,3,6-tetrahydrophthalic anhydride or the appropriate derivative as illustrated below:



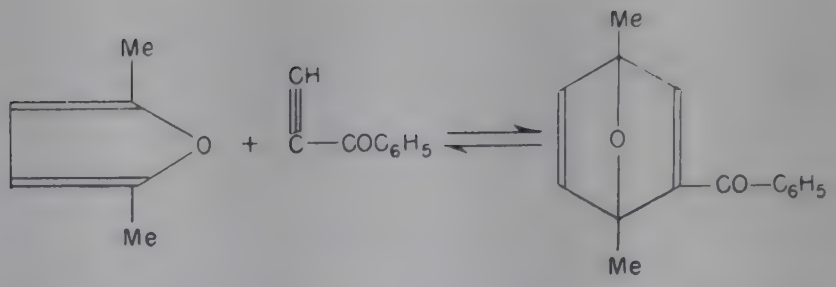
Several other furan types, notably the simple halofurans, furfuryl esters and ethers, and furfural diacetate, react similarly as indicated in Table 3. As will be discussed later, however, certain other types are not adaptable to the diene synthesis.

Acetylenedicarboxylic acid and its esters may be substituted for maleic anhydride. Using equimolecular proportions of furan and methyl acetylenedicarboxylate one obtains 3,6-oxy-3,6-dihydrophthalic ester (I), which will add a second, and even a third molecule of furan to give (II) and (III), respectively.[299, 296]

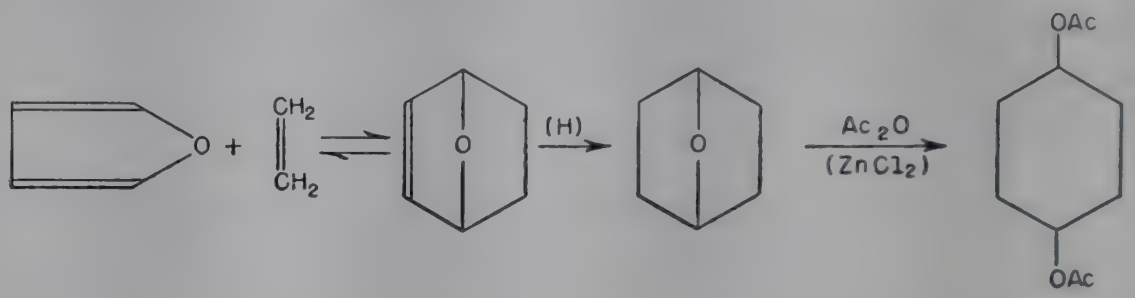


3,6-Oxy-1,2,3,6-tetrahydrophthalonitrile and several of its derivatives have been described as products of the addition of fumaronitrile to various furan compounds,[300] and phenyl ethynyl ketone has been shown to possess sufficient dienophilic activity to form a normal adduct with 2,5-dimethylfuran.[209] In the latter instance the product isolated was 2,5-oxy-2,5-dimethyl-2,5-dihydrobenzophenone.

[299] Diels and Olsen, *J. prakt. Chem.*, **156**, 285 (1940).
[300] Mowry, *J. Am. Chem. Soc.*, **69**, 573 (1947).



To a small degree furan undergoes the Diels-Alder reaction with ethylene at elevated temperature and pressure, with the formation of 1,4-oxy-1,2,3,4-tetrahydrobenzene (b.p. 118–119°; n_D^{20} 1.4629) which was reduced and acetylated as indicated below.[301]



Earlier, Diels and Olsen[299] had called attention to what appeared to be a very unstable adduct of acetylene and 2,5-dimethylfuran. This was refuted by Schenck[260] who demonstrated that no reaction takes place if precautions are taken to exclude oxygen; that the unstable adduct of Diels and Olsen was formed by addition of oxygen to the furan ring. However, in view of the results with ethylene[301] it is possible that under more strenuous reaction conditions acetylene could be made to add to certain furan types to form cyclic adducts.

TABLE 3. FURANS IN THE DIENE SYNTHESIS

Furan compound	Adduct m.p. (°C.)	Ref.
With maleic anhydride		
Furan	125–126	299, 295; see also 302, 296
2-Methylfuran	80, 84	297, 67
3-Methylfuran	82	67
2-Ethylfuran	97–98	303
2-Benzylfuran	102–102.5	304
2-Phenethylfuran	73–74	86
2-(2-*m*-Methoxyphenylethyl)-furan	78–80	86
2-Tetrahydrofurfurylfuran	94.5–95	305
2-Vinylfuran*	150	306
Phenylfurfurylacetylene	112	19

* Addition in this instance is to the conjugated system made up by the double bond in the side chain and the adjacent nuclear double bond (see text).

[301] Nudenberg and Butz, *J. Am. Chem. Soc.*, **66**, 307 (1944).

TABLE 3—*Continued*

Furan compound	Adduct m.p. (°C.)	Ref.
2,5-Dimethylfuran	78	295, 297
2-Methyl-5-isopropylfuran	77	183
2-Methyl-5-*sec*-butylfuran	72	78
2-Propyl-3-ethyl-5-methylfuran	51.5–52.5	209
2-Bromofuran	116	307
3-Bromofuran	131.5–132	307
2-Iodofuran	118–119	308
Furfuryl methyl ether	97	307
Furfuryl acetate	114	296
Furfurylidene diacetate	126.5–127	307
Furfurylacetone	86–87	307
(5-Methylfurfuryl)acetone	84	78
1-Phenyl-3-(5-methyl-2-furyl)-1-propanone	109	78
1-(5-Methyl-2-furyl)-5-methyl-3-hexanone	70–71	309
1-(5-Methyl-2-furyl)-5-methyl-4-hexen-3-one	82–84	309
2,5-Bis(3-oxobutyl)furan	88	78
2,5-Bis(3-oxo-5-methyl-4-hexenyl)furan	88	309
3-(5-Methyl-2-furyl)butyraldehyde	84–85	78
3-(2-Furyl)propionic acid	96	310
Ethyl 3-(2-furyl)propionate	90	310
With fumaronitrile		
Furan	111	300
2-Methylfuran	100	300
2,5-Dimethylfuran	72	300
Furfuryl acetate	113	300
With methyl acetylenedicarboxylate		
Furan	b.p. 130–135 (0.9 mm.)	299; see also 296, 311
With methyl benzoylacetylenecarboxylate		
Furan	b.p. 80 (10^{-4} mm.) n_D^{20} 1.5666	312
With phenyl ethynyl ketone		
2,5-Dimethylfuran	89	209

[302] Bruchhausen and Bersch, *Arch. Pharm.*, **266**, 697 (1928).

[303] Paul, *Bull. soc. chim.*, **10**, 163 (1943).

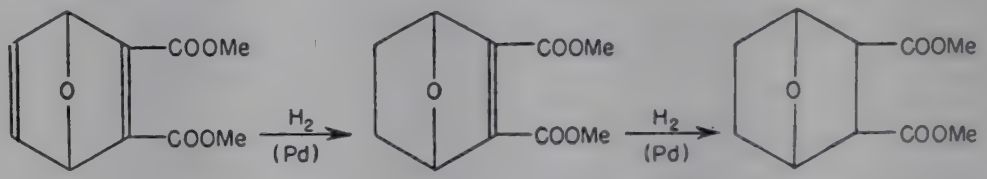
[304] Straley, *Iowa State Coll. J. Sci.*, **11**, 115 (1936).

[305] Kondo, Suzuki and Takeda, *J. Pharm. Soc. Japan*, **55**, 741 (1935); *C. A.*, **29**, 7324 (1935).

[306] Paul, *Compt. rend.*, **208**, 1028 (1939).

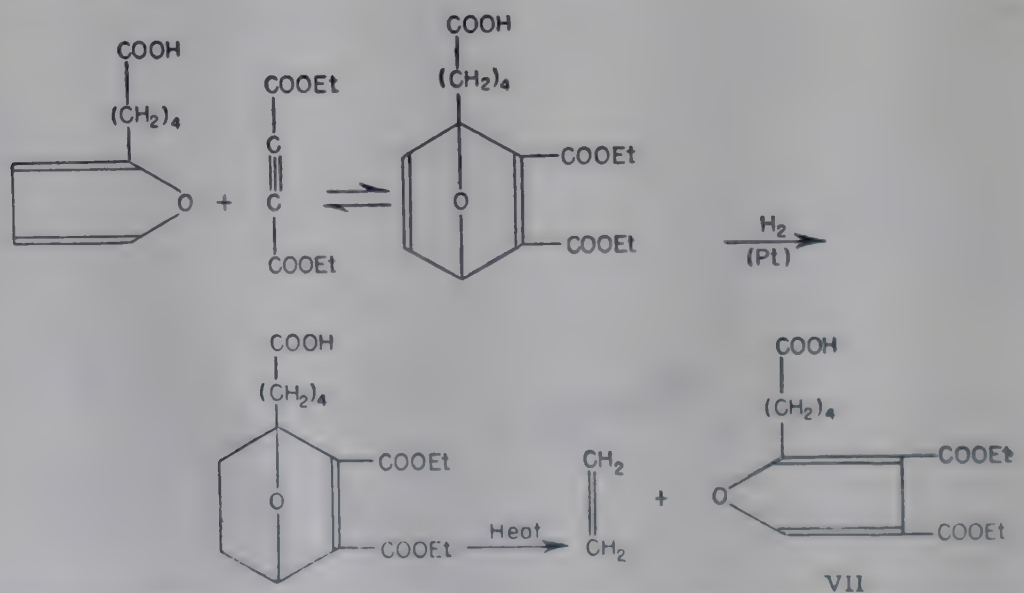
The furan adducts are less stable than those formed from cyclopentadiene but, like the latter, they dissociate on heating with regeneration of the original reactants. The addition product from maleic anhydride and 2-phenethylfuran, for example, decomposes into its generators with great ease even in solution, so that purification necessitates recrystallization at low temperature.[86]

Despite this great tendency toward dissociation the furan adducts can, in most instances, be reduced successfully with hydrogen at low temperature using such catalysts as colloidal palladium or platinum black. In this way the adduct from furan and maleic anhydride gives rise to norcantharadin (3,6-oxyhexahydrophthalic anhydride)° [295, 302, 299]; also obtainable, as the di-ester, VI, by the complete reduction of IV, the 1:1 adduct of furan and acetylenedicarboxylic ester.[299] In the latter instance, if the reaction is stopped after absorption of only one mole of hydrogen, the product is ethyl 3,6-oxy-3,4,5,6-tetrahydrophthalate, V.[296, 299]



IV V VI

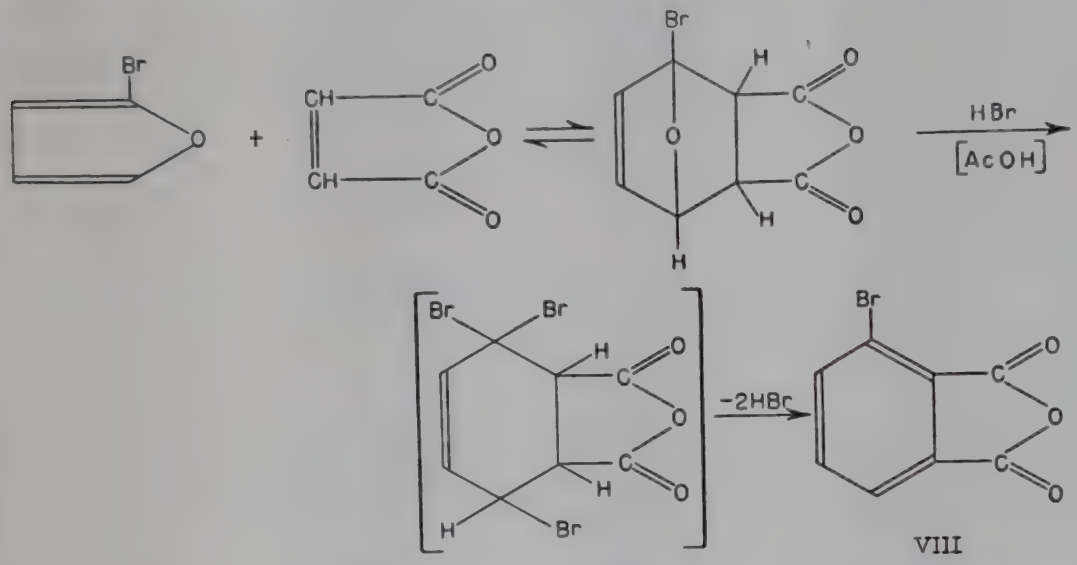
The partially hydrogenated adduct, V, is heat labile, and decomposes on attempted distillation into ethylene and ethyl 3,4-furandicarboxylate.[311] This reaction was adapted later by Hofmann[313] (see also [63]) for the synthesis of 5-(3,4-dicarbethoxy-2-furyl)valeric acid, VII, by similar decomposition of the partially reduced adduct of 5-(2-furyl)valeric acid and ethyl acetylenedicarboxylate.



VII

° For discussion of the three stereoisomeric forms of 3,6-oxyhexahydrophthalic acid, see Woodward and Baer.[294]

On heating the furan-(maleic anhydride) adducts with hydrobromic acid in glacial acetic acid, the oxygen bridge is ruptured and dehydrobromination follows with the direct formation of phthalic acid or substituted derivatives of this acid. Since the orientation of the substituents in the resulting phthalic acids is known, Van Campen and Johnson[307] proposed this transformation as an absolute method for establishing the position of substituents in the furan ring of those furan compounds which form adducts with maleic anhydride. Thus, 2-bromofuran was converted into 3-bromophthalic anhydride, VIII, and by a similar sequence of reactions, the isomeric 3-bromofuran gave rise to 4-bromophthalic anhydride.[307]



VIII

As expected, the hydrogenated adducts of furans with maleic anhydride, and also the partially or completely hydrogenated adducts derived from furans and acetylenedicarboxylic ester are similarly attacked by halogen acids with cleavage of the oxygen bridge, and formation of an intermediate dihalotetrahydrophthalic acid. The latter is subject to facile dehydrohalogenation, the more so when the carbon atoms of the original bridge carry alkyl substituents.[295] Thus, the reduced furan-(maleic anhydride) adduct, IX, gives rise to 1,2-dihydro- (X), or 4,5-dihydrophthalic acid (XI)[p] in accordance with the reaction sequence illustrated below. The

[p] While the configuration of the product has not been elucidated, XI would seem to be favored over X on theoretical grounds. That is, formation of XI involves α,β-dehydrohalogenation with respect to the carboxyl groups, and this would be expected to occur preferentially to β,γ-elimination (to form X) where both routes are possible.

[307] Van Campen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

[308] Johnson, Van Campen and Grummitt, *J. Am. Chem. Soc.*, **60**, 111 (1938).

[309] Nazarov and Nagibina, *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, **1946**, 641; *C. A.*, **42**, 7736 (1948).

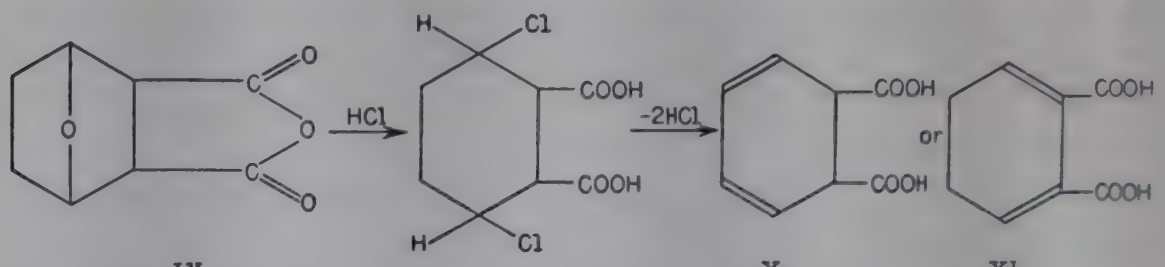
[310] Herz, *J. Am. Chem. Soc.*, **68**, 2732 (1946).

[311] Alder and Rickert, *Ber.*, **70**, 1354 (1937).

[312] Shen and Whiting, *J. Chem. Soc.*, **1950**, 1772.

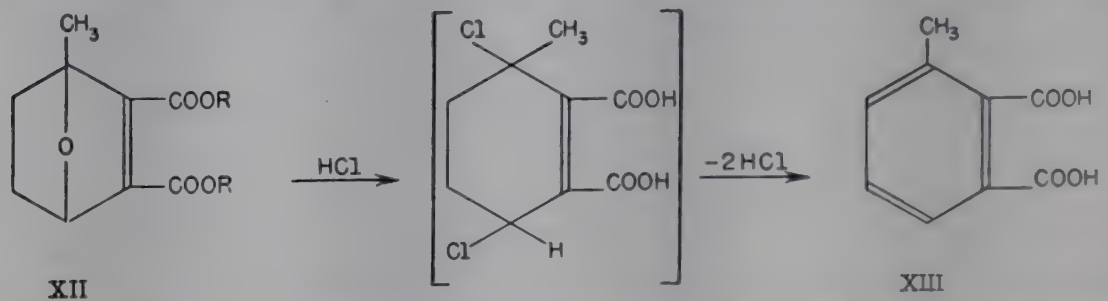
[313] Hofmann, *J. Am. Chem. Soc.*, **66**, 51 (1944).

hydrogenated adduct derived from 2,5-dimethylfuran and maleic anhydride shows a similar behavior, but the intermediate compound undergoes spon-



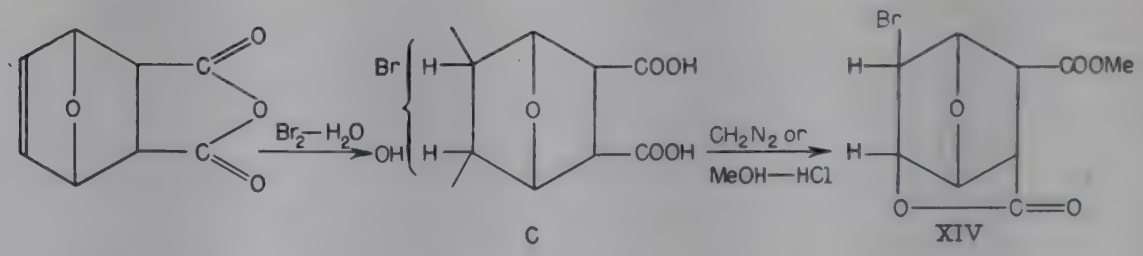
IX X XI

taneous dehydrohalogenation in the medium of its formation, giving rise to 3,6-dimethyl-4,5(or 1,2)-dihydrophthalic acid.[295] Under the same conditions XII, the partially reduced adduct of 2-methylfuran and methyl acetylenedicarboxylate is converted into 3-methylphthalic acid, XIII.[311]



XII XIII

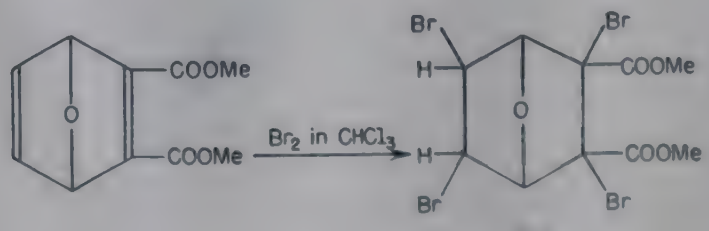
Hypobromous acid adds to the adduct of furan and maleic anhydride to give a bromohydrin (C) which lactonizes readily to form XIV.[q 296] In like



C XIV

manner, bromohydrins have been obtained from the adducts of various furan homologs with maleic anhydride.[297, 86]

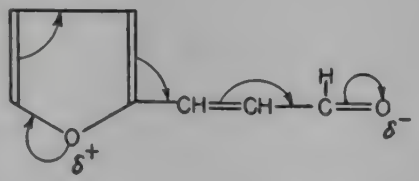
The action of dry bromine on the adduct of equimolar quantities of furan and methyl acetylenedicarboxylate results in addition to both double bonds with formation of methyl 3,6-oxy-1,2,4,5-tetrabromohexahydrophthalate, XV.[299]



XV

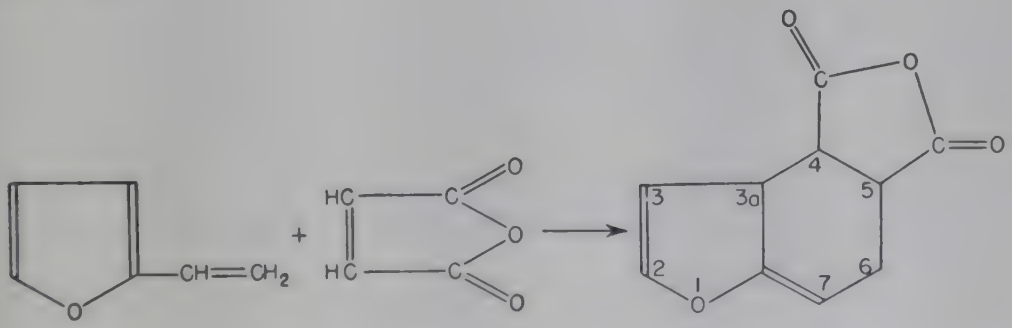
[q] The chemistry of the reactions involved is described by Woodward and Baer.[294]

As mentioned previously, certain furan compounds fail to participate in the Diels-Alder reaction. For example, Herz has shown that 3-(2-furyl)-acrolein, 3-(2-furyl)acrylic acid, and 2-(2-nitrovinyl)furan fail to form adducts with maleic anhydride.[310] He offers an explanation based on the mechanism proposed by Hudson and Robinson[314] which suggests initiation of the Diels-Alder reaction by ionic centers; the diene acting as an electron donor (nucleophilic activity), and the dienophile as an electron acceptor (electrophilic activity). In the three furan compounds under consideration, the strongly electrophilic groups attached to the terminal carbon atom of the ethylenic substituent deactivate this carbon atom and, by virtue of conjugation, the nucleus:



Herz reasoned that if the conjugation were destroyed by saturation of the side chain, reaction with maleic anhydride would proceed normally. This postulate was borne out experimentally using 3-(2-furyl)propionic acid.[310]

2-Vinylfuran possesses no terminal electrophilic group to interfere, and as expected, it adds maleic anhydride.[306] However, careful examination of the behavior of the adduct led Paul[303] to assign to it the structure of 3a,4,-5,6-tetrahydro-4,5-benzofurandicarboxylic anhydride, XVI. This product would represent 1,4-addition to the conjugated system comprising the double bond of the side chain and the adjacent nuclear double bond as indicated below:



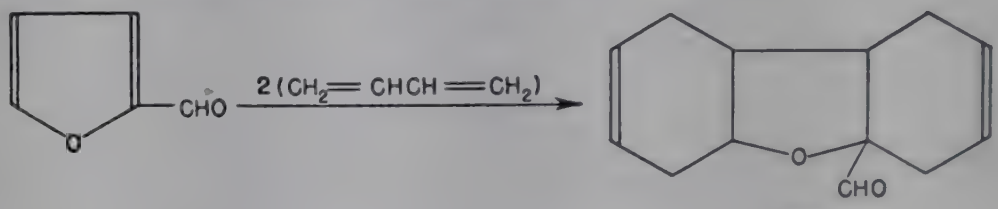
XVI

Thus, of the two dienic systems in 2-vinylfuran, that involving the side chain is the more active. This behavior is related to that of certain styrene derivatives which undergo 1,4-addition reactions involving the vinyl group and the adjacent double bond of the benzene ring.[293]

The failure of furfural to act as a diene when treated with maleic anhydride is apparently due to the effect of the aldehyde group in diminishing

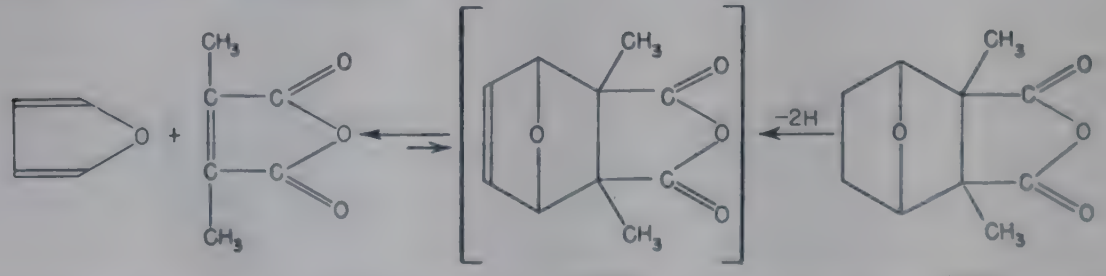
[314] Hudson and Robinson, *J. Chem. Soc.*, **1941**, 715.

the electron-donor properties of the nucleus. When this effect is destroyed, as in conversion of furfural to its diacetate, an adduct is obtained in the normal manner.[307] However, while furfural apparently shuns the dienic role in the diene synthesis, recent experimental work indicates that, in some instances, it may take the dienophilic role. Under the influence of heat, furfural slowly adds two molecules of butadiene to form a liquid aldehyde, the composition of which corresponds to $C_{13}H_{16}O_2$. The structure of this product has not been established unequivocally, but it has been assigned that of 2,3:4,5-bis-2-butenotetrahydrofurfural, XVII, formed by what is typically a Diels-Alder reaction.[r 315, 316] It might be anticipated that other furans possessing electron-withdrawing substituents (e.g., 2-nitrofuran, 2-furoic acid and ester) could be made to react in a similar manner with suitable dienes under certain conditions.



XVII

In general, it appears that furan compounds possessing strongly electrophilic groups fail to react as dienes in the Diels-Alder reaction, even with the strongly dienophilic maleic anhydride. As a matter of fact, when weaker dienophiles are employed, the conjugate system of furan itself is not sufficiently reactive to permit addition to occur. For example, attempted reaction of furan with dimethylmaleic anhydride (pyrocinchonic anhydride) has failed under a variety of conditions.[299, 302] The objective of this work was the synthesis of the physiologically active cantharidin, XIX, by hydrogenation of the expected adduct, XVIII. However, the equilibrium appears to be completely in favor of the dissociation products so that no adduct can be isolated. This viewpoint is supported by the fact that XIX is converted into furan and dimethylmaleic anhydride when subjected to dehydrogenation.[302] Presumably this dissociation occurs through the intermediate dehydrocantharidin, XVIII.



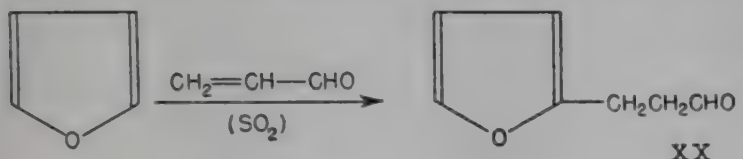
XVIII XIX

[r] A mechanism for this reaction is presented elsewhere (p. 663).

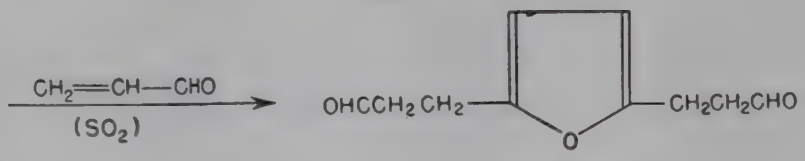
[315] Hillyer, Swadesh, Leslie and Dunlop, *Ind. Eng. Chem.*, **40**, 2216 (1948).

[316] Herbolsheimer (to Phillips Petroleum Co.), U. S. Pat. 2,483,903 (1949); *C. A.*, **44**, 2565 (1950).

Furan and its single homologs likewise fail to react directly with such dienophiles as vinyl phenyl ketone,[317] β-nitrostyrene,[318, 319] acrolein, crotonaldehyde and the like. On the other hand, it has been found that in the presence of certain catalysts, a "substitution-addition" type of reaction occurs with formation of non-cyclic adducts similar to those encountered in the pyrrole series. Thus, Sherlin and co-workers[320] report that furan combines with one or two molecules of acrolein under the influence of a small amount of sulfur dioxide. In this reaction, the hydrogen atoms in the 2-, and 5-positions are displaced from the nucleus to the double bond of acrolein to form 3-(2-furyl)propionaldehyde, XX, and 2,5-furandipropionaldehyde, XXI, respectively, as illustrated below (see also p. 415). Later,

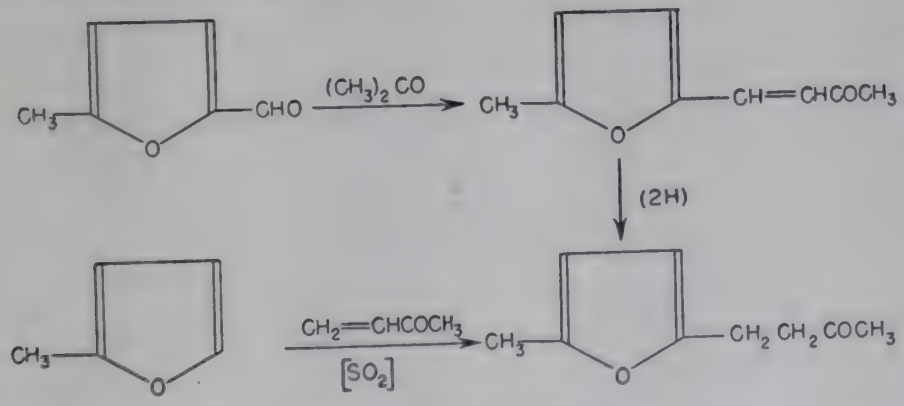


XX



XXI

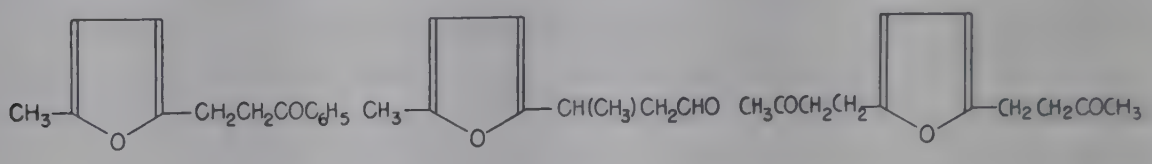
Alder and Schmidt[78] (see also [309]) found that a variety of acidic catalysts (sulfur dioxide, sulfuric acid, hydrochloric acid, benzenesulfonyl chloride, among others) were effective in this type of reaction, and described similar adducts from furan and 2-methylfuran with other α,β-unsaturated carbonyl compounds. For example, an equimolecular mixture of 2-methylfuran and methyl vinyl ketone, which remains unchanged after standing for some weeks, was found to react spontaneously upon addition of a few drops of aqueous sulfur dioxide to give (5-methylfurfuryl)acetone, XXII, the struc-



XXII

[317] Allen, Bell, Bell and Van Allan, *J. Am. Chem. Soc.*, **62**, 656 (1940).
[318] Allen and Bell, *J. Am. Chem. Soc.*, **61**, 521 (1939).
[319] Allen, Bell and Gates, *J. Org. Chem.*, **8**, 373 (1943).
[320] Sherlin, Berlin, Serebrennikova and Rabinovich, *J. Gen. Chem. U. S. S. R.*, **8**, 7, 16, 22 (1938); *C. A.*, **32**, 5397 (1938).

ture of which was proven by its synthesis from 5-methylfurfural as shown above. Under similar conditions, phenyl vinyl ketone reacted with 2-methylfuran to form 1-phenyl-3-(5-methyl-2-furyl)-1-propanone, XXIII; crotonaldehyde gave rise to 3-(5-methyl-2-furyl)butyraldehyde, XXIV. Furan, with its two open alpha positions, added two molecules of methyl vinyl ketone with formation of 2,5-bis(3-oxobutyl)furan, XXV.[78]



XXIII XXIV XXV

Nuclear Substitution Reactions

The substitution reactions commonly associated with aromatic types have been applied to furans at one time or another, and with varying success. In general, the furans display greater reactivity and variability of behavior than their benzene analogs. For the most part the heterocyclic nucleus lacks the integrity of the benzene ring, and reagents which are sufficiently active to effect substitution all too frequently promote side-reactions leading to polymeric products. As a consequence, much effort has been expended in a search for mild reagents and experimental conditions to minimize the undesired reaction(s).

Such reactions as halogenation, nitration and metalation are discussed in appropriate chapters dealing with the type of product obtained. Our concern here, is with the other substitution reactions of furan and its homologs.

The Friedel-Crafts Reaction. No doubt as a consequence of their sensitivity to the condensing agents commonly employed, there is comparatively little reported work on attempted alkylation of furan and its homologs by the Friedel-Crafts procedure (see [321]). The difficulty lies in the fact that catalysts for the reaction also catalyze resinification which, depending upon experimental conditions, may involve formation of a film or coating on the surface of the condensing agent which acts to inhibit further reaction, or may become so extensive that no simple products can be isolated. In the latter instance, it is important to note that while alkylation may have occurred to a considerable extent, the furan homolog so formed is at least equally susceptible to polymerization as the starting compound. The course of the

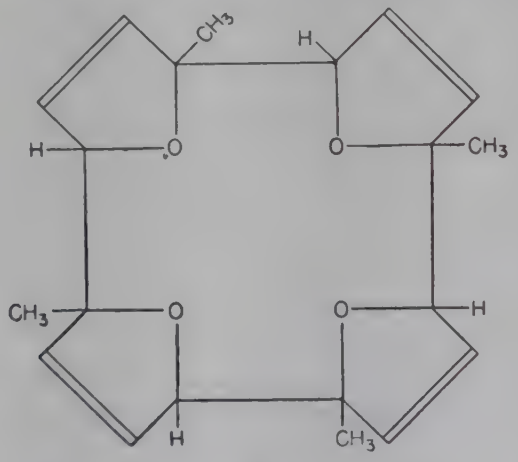
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[321] Calloway, *Chem. Revs.*, **17**, 327 (1935).
[322] The Quaker Oats Company, unpublished work.
[323] Brown, Thesis, Iowa State College, 1947.
[324] Rueggeberg, Cushing and Cook, *J. Am. Chem. Soc.*, **68**, 191 (1946).

resinification reaction[s] is obscure, but appears to go forward by way of an intermediate addition compound[t] of the particular furan compound and metal halide ($SnCl_4$, $AlCl_3$, etc.). When an excess of the furan is available, the addition compound slowly dissolves with ensuing polymerization.

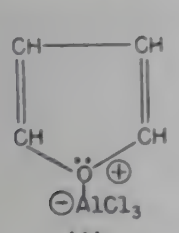
Brown[323] attempted to alkylate 2-methylfuran with isopropyl alcohol under the influence of chlorosulfonic acid, a procedure which has been applied with success in the benzene series.[324] Rapid tar formation occurred, resulting in the formation of a brittle, sponge-like material. He also investigated the action of *n*-butyl bromide on 2-methylfuran, using boron fluoride as the condensing agent and, as before, the sole product was resin. Recently, however, furan had been alkylated successfully by trimethylethylene and boron fluoride at 10–35°. From the reaction mixture, mono- (17 per cent), and di-*t*-pentylfuran (3 per cent) were obtained.[62] Mono- (46 per cent), and dihexenylfuran (2 per cent) were similarly derived from furan and 2-methyl-

[s] The action of boron fluoride on 2-methylfuran has, under controlled conditions, given rise to a light colored polymer mixture from which a pure, tetrameric product ($C_{20}H_{24}O_4$; b.p. 149°–150°; 0.37–0.38 mm.) has been isolated. While the configuration of this product has not been definitely established, structure I has been tentatively assigned.[322] Its formation can be accounted for by way of an intermediate complex related to B (footnote[t]).

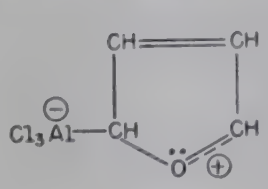


I

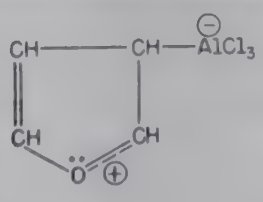
[t] Such a complex of metal halide (e.g., $AlCl_3$) with the furan nucleus can be drawn in three different forms, A, B, and C (see also p. 643). In the Friedel-Crafts alkylation



(A)



(B)

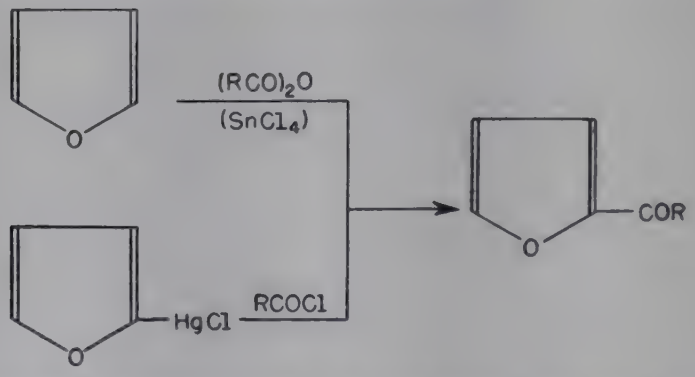


(C)

with alkyl halides, such coordination would be in competition with the reaction: $RCl + AlCl_3 \rightleftharpoons R^+ + AlCl_4^-$. With furan types which possess electron-withdrawing substituents, one would anticipate a decreased electron-donor tendency in the nucleus, and therefore less interference with alkylation reaction. In accordance with this viewpoint is the successful alkylation of such furan types as furfural and furoic ester by alkyl halides in the presence of aluminum chloride (see pp. 340, 498).

pentadiene[62] (see also [325, 326]). Presumably in both instances the orientation is that normally encountered in the furan series, namely, α-substitution where such a location is open.

The synthesis of furyl ketones by Friedel-Crafts acylation of furan and its homologs is readily accomplished. No doubt the success of this reaction is related, at least partially, to the greater product stability as compared to that obtaining in the alkylation reaction. Both acid anhydrides and chlorides have been employed, although the former appear to give better results.[327, 328] In either instance, it is beneficial to minimize contact of the unreacted furan with the condensing agent as, for example, by employing an ample quantity of solvent and/or by incremental addition of the furan to the reaction mixture. Additionally, elevated temperatures are detrimental from the standpoint of product yield. Thus, condensation of furan with acetic anhydride in the presence of zinc chloride at 0–20° gave rise to furyl methyl ketone in 66 per cent yield, whereas the yield at 30–60° was only 40 per cent.[329] As expected, the incoming acyl group orients to an α-carbon if such is available; the ketones derived from furan itself were shown to be identical to those obtained by reaction of the known 2-furylmercuric chloride with the appropriate acid chloride.[71]



The relative ease of substitutions of the furan nucleus is evidenced by the preferential acylation of furan and its homologs in benzene solution. Actually, acetylation of 2,5-dimethylfuran, which involves β-substitution of the ring, may even be carried out in toluene with very little attack on the solvent.[304] Yet another illustration is apparent in the results of a recent study wherein iodine was used to catalyze acylation of certain aromatic types. Reaction failed when applied to alkylbenzenes, and while it was

[325] Appleby, Lovell and Love (to Shell Development Co.), U. S. Pat. 2,429,575 (1947); *C. A.*, **42**, 1313 (1948).

[326] Matuszak (to Phillips Petroleum Co.), U. S. Pat. 2,432,482 (1947); *C. A.*, **42**, 2421 (1948).

[327] Gol'dfarb and Smorgonskii, *J. Gen. Chem. U. S. S. R.*, **8**, 1523 (1938); *C. A.*, **33**, 4593 (1939).

[328] Hartough and Kosak, *J. Am. Chem. Soc.*, **68**, 2639 (1946).

[329] Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 1012 (1947).

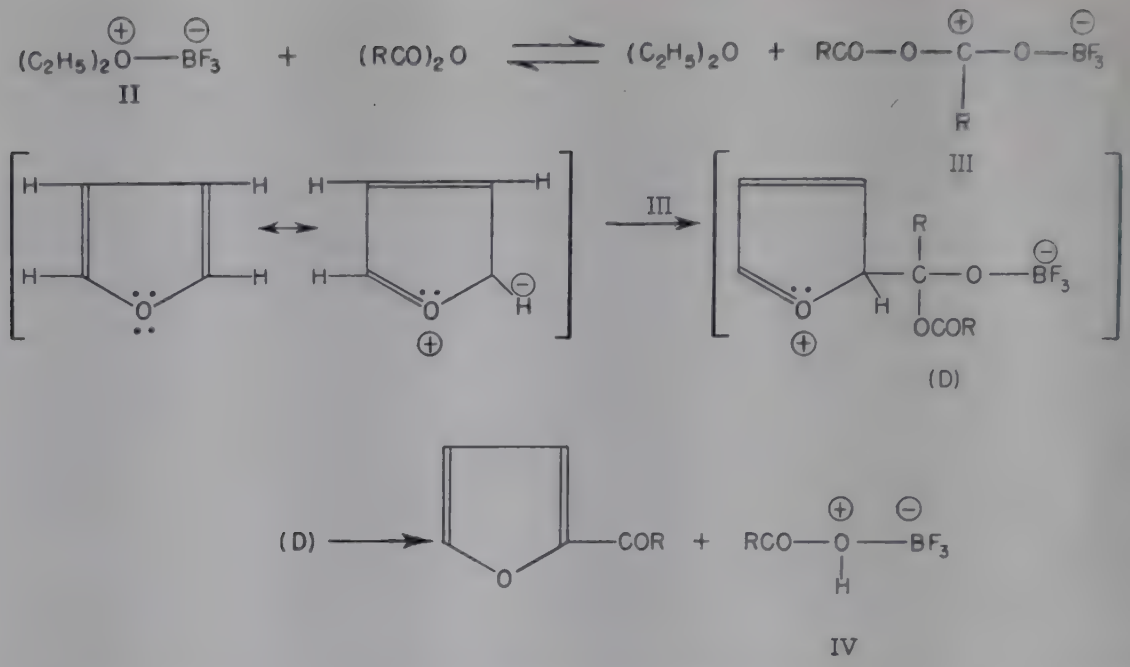
successful with more reactive benzene types (e.g., anisole, acetanilide), it necessitated higher temperatures and a greater concentration of iodine than were required to effect acylation of furan.[330]

As indicated elsewhere (p. 422), a variety of condensing agents have been used. According to Calloway[330a] the general order of decreasing usefulness of several metal chlorides is: $SnCl_4$, $FeCl_3$, $AlCl_3$, $TiCl_4$. Also effective are zinc chloride[39] and mercuric chloride.[163] In general, such catalysts have been employed in molar quantity equivalent to the acylating agent. More recent work, however, has revealed the effectiveness of catalytic amounts of iodine, hydriodic acid, zinc chloride and orthophosphoric acid in promoting the condensation of acid anhydrides with furan.[328, 329] In these instances, the catalyst concentration may be quite critical. Although 4×10^{-5} mole of iodine per mole of acetic anhydride failed to bring about acetylation, 4×10^{-4} mole resulted in a very rapid reaction which produced furyl methyl ketone in 60 per cent yield. Increase in the iodine concentration beyond this value reduced the product yield, which became negligible when acetyl chloride was used in place of the anhydride. Using hydriodic acid at a concentration of 0.01 mole per mole of acetic anhydride, reaction with furan proceeded vigorously, giving rise to the appropriate ketone in 76 per cent yield, as high as has been reported to date. Also formed was a small amount of what may have been 2,5-diacetylfuran. It was suggested that a lower concentration of hydriodic acid might be productive of yet higher yields of the monoketone. It remains to be determined whether or not iodine and hydriodic acid will promote the acylation of 2-furoic esters and other negatively substituted furans.

Deserving of special mention is the recent work of Hartough and Levine and their co-workers on the effectiveness of catalytic amounts of boron fluoride complexes in bringing about the acylation of furan and its homologs with acid anhydrides (p. 422). The procedure is relatively simple, and involves addition of the catalyst to the other components held at 0° in an ice-bath. The heat of reaction is rapidly dissipated, following which the mixture is stirred for an additional thirty minutes at room temperature, and then worked up to give the appropriate furyl ketone in excellent yield. The following mechanism was proposed[331] to account for the activity of boron fluoride etherate.

According to this scheme the etherate II reacts with the anhydride to give the new complex III, which then condenses with furan to give D. Decomposition of D produces the furyl ketone together with IV, the com-

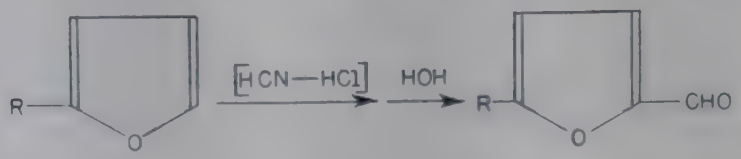
[330] Chodroff and Klein, *J. Am. Chem. Soc.*, **70**, 1647 (1948).
[330a] Calloway, *Iowa State Coll. J. Sci.*, **9**, 141 (1934).
[331] Heid and Levine, *J. Org. Chem.*, **13**, 409 (1948).



plex of boron fluoride with the appropriate aliphatic acid. It was further postulated that IV, being continuously recycled, was the actual condensing agent; that IV takes over the function of II in the first step, thereby explaining why catalytic quantities of II are productive of high yields of furyl ketones. In support of this mechanism, further work revealed that IV (where R = CH_3) could be substituted for II with practically the same result.[332]

The Gattermann Aldehyde Synthesis. The Gattermann reaction, which introduces an aldehyde group by the action of hydrogen cyanide and hydrogen chloride, may be regarded as a special case of acylation wherein one of the radicals of the carbonyl group is hydrogen. It was studied extensively by Reichstein as a means of ascertaining the relative reactivities of several ring systems. He concluded that, of the single five-membered heterocyclic compounds, pyrrole is more reactive than furan, which is more readily substituted than thiophene.[74]

Reaction occurs readily when hydrogen chloride is passed into a cold, ether solution of furan and dry hydrogen cyanide. Hydrolysis of the intermediate product gave rise to furfural which was isolated in 35 per cent yield. Similarly, 2-methyl- and 2-ethylfuran yielded the corresponding 5-alkylfurfurals, but thiophene did not react without a catalyst ($AlCl_3$).[74]



Applied to 3-methylfuran which has two available α-positions, the reaction proceeded with formation of 3-methylfurfural, the identity of which was

[332] Levine, Heid and Farrar, *J. Am. Chem. Soc.*, **71**, 1207 (1949).

proven by oxidation to the known 3-methyl-2-furoic acid.[203] No other aldehydic product was found, hence it appears that a β-methyl group directs an incoming aldehyde group exclusively to the adjacent alpha nuclear position when such location is unoccupied.

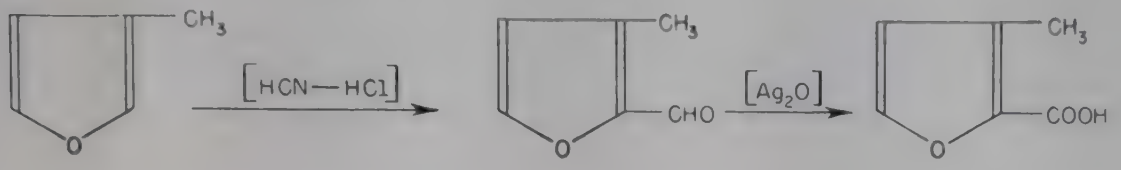


TABLE 4. ALDEHYDE SYNTHESES BY THE GATTERMANN REACTION

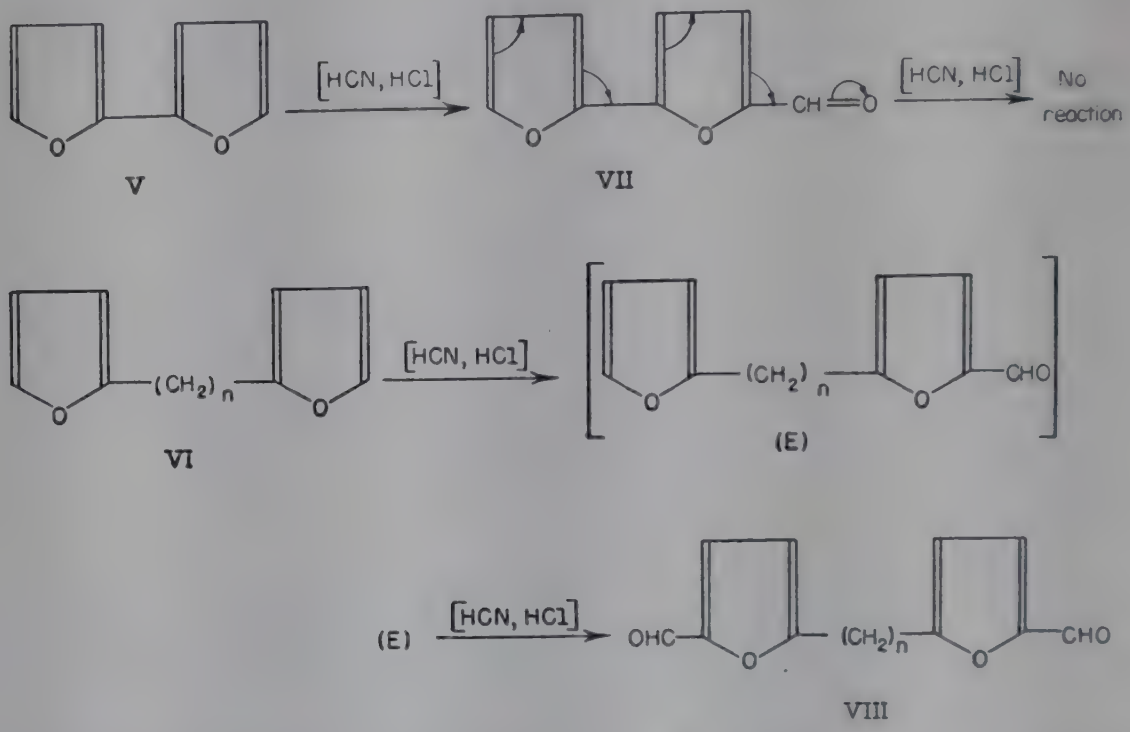
Starting material	Product	Yield (%)	Ref.
Furan	furfural	35	74
2-Methylfuran	5-methylfurfural	60	74
2-Ethylfuran	5-ethylfurfural	53	74
2-*i*-Propylfuran	5-*i*-propylfurfural	40	70
3-Methylfuran	3-methylfurfural	56	203
2,3-Dimethylfuran	4,5-dimethylfurfural	22	76
2,4-Dimethylfuran	3,5-dimethylfurfural	12	203
3,4-Dimethylfuran	3,4-dimethylfurfural	15	76
2,3,4-Trimethylfuran	3,4,5-trimethylfurfural	32	75
2,2′-Bifuryl	5-(2-furyl)furfural	45	333
2,2′-Difurylmethane	5-methylenedifurfural	18	333
sym-2,2′-Difurylethane	5-ethylenedifurfural	—	74

To date there has been no report of the direct introduction of an aldehyde group into the furan nucleus at a β-position. As indicated in Table 4, only α-furaldehydes have been isolated. When the reaction was attempted with 2,5-dimethylfuran, no aldehydic product could be found. On working up the reaction mixture some acetonylacetone was isolated, presumably as a consequence of acid-hydrolysis of the original furan compound.[74] Reaction also failed to occur with certain other furan types. Thus, ethyl furoate and coumarone were largely recovered unchanged,[74] as was 2-methyl-3-furoic ester, even when a catalyst was employed in an effort to promote condensation.[330a] Reichstein concluded that furans participate in the Gattermann aldehyde synthesis except (1) when both alpha positions are occupied and (2) when an electron-withdrawing substituent is attached to the nucleus. By contrast, compounds of the pyrrole series react irrespective of the nature of substituent groups.[74]

The results obtained with 2,2′-bifuryl, V, and its homologs, VI, are of some interest. Condensation of V with (hydrogen cyanide-hydrogen chloride)-reagent gave only the monosubstitution product, 5-(2-furyl)furfural (VII), even when a large excess of the reagent was employed.[333] On the other hand, 2,2′-difurylmethane (VI; $n = 1$),[333] and *sym*-di-2-furylethane (VI,

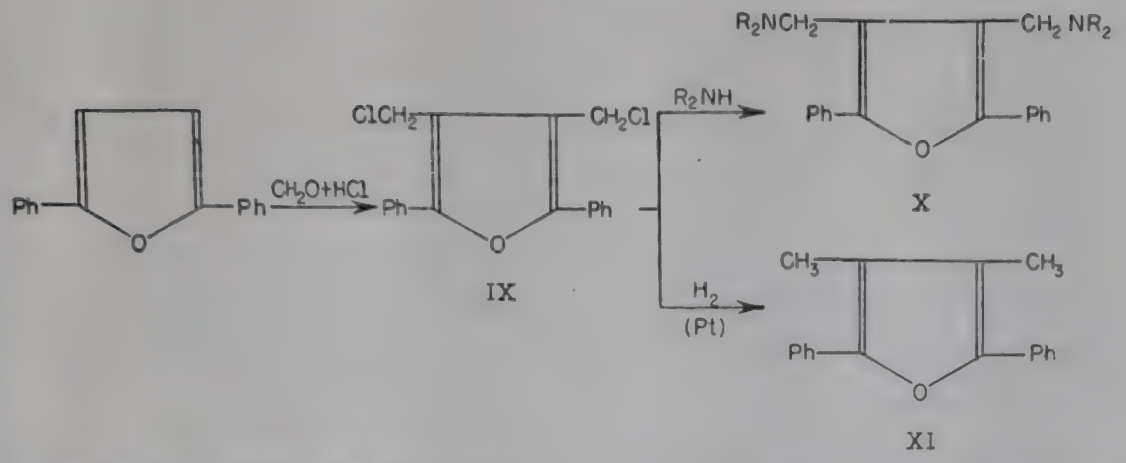
[333] Reichstein, Grüssner and Zschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).

$n = 2$)[74] substituted twice under these conditions to form the corresponding dialdehydes, VIII. It would appear from this evidence that the deactivating effect of an electrophilic group (in this instance CHO) is transferred through the extended conjugated system of VII, thereby inhibiting reaction in the adjacent nucleus. Due to interruption of the conjugation no similar effect is possible in aldehydes possessing the structure indicated by E; each nucleus reacts more or less independently, and disubstitution occurs readily.[u]

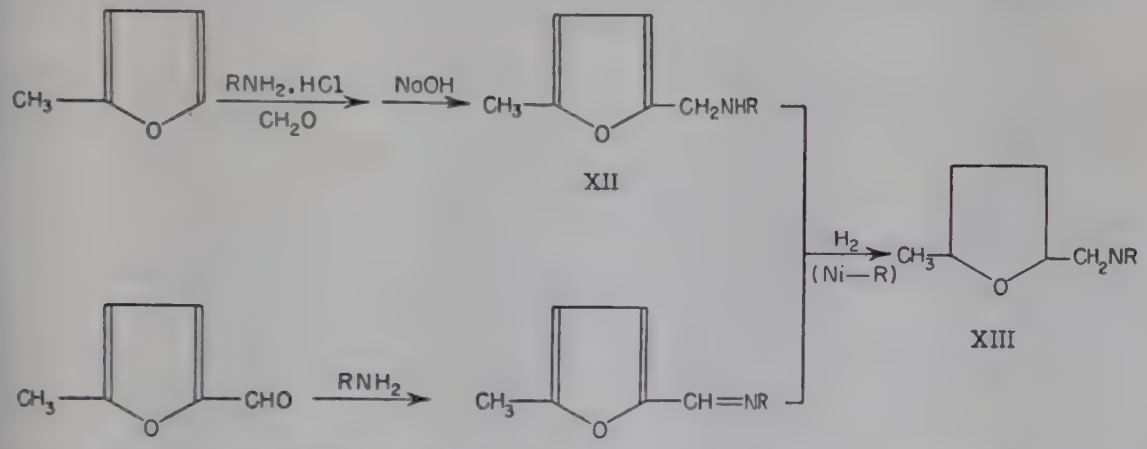


Halomethylation and Aminomethylation. The halomethylation reaction has not been applied to furan or the alkylfurans, and would probably be unsuccessful in view of their sensitivity to the highly acidic conditions involved. However, the direct introduction of chloromethyl and bromomethyl groups has been achieved with the more stable 2,5-diarylfurans.[225, 226] Treatment of these with a solution of paraformaldehyde in hydrobromic and acetic acids gives rise to 3-bromomethyl-2,5-diarylfuran, substitution being confined to the reactive furan nucleus. The related chloromethylation reaction with 2,5-diphenylfuran led to the disubstitution product, 3,4-bis(chloromethyl)-2,5-diphenylfuran (IX) which, by the action of secondary amines, was converted into the corresponding bis-(aminomethyl) compound, X. With hydrogen, over a platinum catalyst, IX undergoes hydrogenolysis to form 3,4-dimethyl-2,5-diphenylfuran, XI.

[u] According to this concept, *sym*-di-2-furylethylene which, like V, possesses a completely conjugated system should substitute only once in the Gattermann synthesis, under the conditions employed by Reichstein.



Related to this is the Mannich reaction, or the direct introduction of an aminomethyl substituent, which has been successfully applied to 2-methylfuran for the synthesis of a variety of 5-methylfurfurylamines, XII (p. 237). As expected, substitution occurs at the open alpha position, the orientation being known by virtue of the separate reaction sequences shown below, both leading to the same, crystalline 3,5-dinitrobenzoate of 5-methyltetrahydrofurfurylamine, XIII.[335]



In order to induce condensation with the amine-formaldehyde mixture at moderate temperatures, it is necessary to conduct the reaction in acidic medium,[v] generally by introducing the amine as the hydrochloride[335] or, preferably, the acetate.[337] In the former instance, elevated temperatures promote resinification with consequent loss in product yield[335] which, under certain circumstances, may be in the neighborhood of 90 per cent of the theoretical.[337] To date the reaction has not been successfully carried out with furan, which is more resistant to condensation and failed to react under the conditions employed by Eliel and Peckham.[337] Neither has it been possible to effect aminomethylation of 2,5-dimethylfuran,[337] a reaction which would require β-substitution of the nucleus.

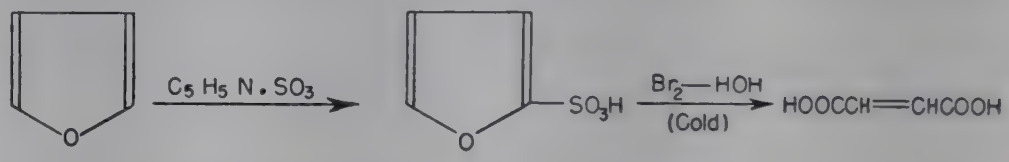
[v] This is also true of the Mannich reaction with thiophene.[336]

[335] Holdren and Hixon, *J. Am. Chem. Soc.*, **68**, 1198 (1946).

[336] Lukasiewicz and Murray, *J. Am. Chem. Soc.*, **68**, 1389 (1946).

[337] Eliel and Peckham, *J. Am. Chem. Soc.*, **72**, 1209 (1950).

Sulfonation. Until a few years ago, sulfonation in the furan series was limited to furoic acid and its halogen-substituted derivatives. Vigorous sulfonating agents, such as fuming sulfuric acid and chlorosulfonic acid can not be used with furan and its homologs due to their facile resinification. Recently, however, Terent'ev and Kazitsyna[338, 339, 340, 341, 342, 343] have reported excellent results with the milder 1-proto-1-pyridinesulfonate.[w] The usual technique involved heating the furan and reagent in ethylene dichloride at 100–110° for 8–10 hours. Under these conditions, furan gave rise to 2-furansulfonic acid (oily liquid; S-benzylthiouronium salt, m.p. 205°), which was isolated as the barium salt in 90 per cent yield. The location of the sulfo group on an α-carbon was demonstrated by oxidation of the salt with cold, aqueous bromine, resulting in the formation of maleic acid.[x] 2-Furansulfonamide, m.p. 122–123.5°, has been obtained by decarboxylation of 5-sulfamyl-2-furoic acid.[344] The isomeric 3-furansulfon-



amide, m.p. 106–108°, is also known; prepared by removal of the bromine atoms from barium 2,5-dibromo-3-furansulfonate (p. 128) and conversion to the amide by way of 3-furansulfonyl chloride.[344]

With 1-proto-1-pyridinesulfonate in ethylene dichloride at 30–40° for several weeks, 2-methylfuran gave rise to 5-methyl-2-furansulfonic acid, XIV (50 per cent yield). Under the conditions described above, however, it was substituted twice with formation of 5-methyl-2,4(?)-furandisulfonic acid, XV (*ca.* 80 per cent yield). Similarly, 2,5-dimethyl-3-furansulfonic acid, XVI, was derived from 2,5-dimethylfuran in 62 per cent yield.

[w] Dr. F. Y. Wiselogle has suggested that the prefix "proto" designates addition of a proton, thus providing a nomenclature for these dipolar compounds. Benzene and its homologs are not sulfonated by this reagent which is, however, active enough to effect substitution of anisole and thiophene.[339]

[x] By analogy with the behavior of α- and β-sulfofuroic acids under the same conditions the absence of a sulfo group in the oxidation product establishes its α-location. β-Sulfo groups are retained in the oxidation product (p. 510).

[338] Terent'ev and Kazitsyna, *Compt. rend. acad. sci. U. R. S. S.*, **51**, 603 (1946); *C. A.*, **41**, 2033 (1947).

[339] Kazitsyna, *Vestnik Moskov. Univ.*, **1947**, No. 3, 109; *C. A.*, **42**, 3751 (1948).

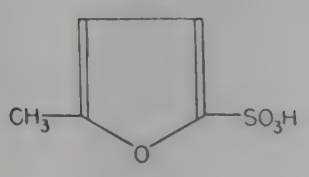
[340] Terent'ev, *Vestnik Moskov, Univ.*, **1947**, No. 6, 9; *C. A.*, **44**, 1480 (1950).

[341] Terent'ev and Kazitsyna, *Compt. rend. acad. sci. U. R. S. S.*, **55**, 625 (1947); *C. A.*, **42**, 556 (1948).

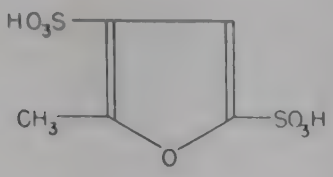
[342] Terent'ev and Kazitsyna, *J. Gen. Chem. U. S. S. R.*, **18**, 723 (1948); *C. A.*, **43**, 214 (1949).

[343] Terent'ev and Kazitsyna, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **19**, 531 (1949); *C. A.*, **43**, 7015 (1949).

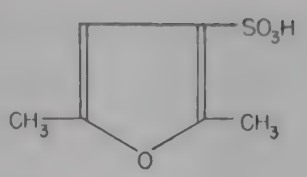
[344] Cinneide, *Nature*, **160**, 260 (1947).



XIV



XV



XVI

No sulfonation occurred when furfural and furfuryl methyl ether were employed under like conditions. On the other hand, furyl methyl ketone was converted in high yield into barium 5-acetyl-2-furansulfonate.[345] With furoic acid in chlorobenzene, sulfonation with 1-proto-1-pyridinesulfonate occurred at 135°, but decarboxylation took place and 2-furansulfonic acid was obtained as the product.[340, 343] Additional work along these lines is described in a later paper by Terent'ev and his associates.[346]

The furansulfonic acids are stable in alkali (compare [347]), but are readily hydrolyzed on heating with aqueous acids with loss of sulfur dioxide. This is in contrast to the behavior of 2-coumaronesulfonic and 2-thiophenesulfonic acids which, under the latter conditions, lose the sulfo group as sulfuric acid with regeneration of coumarone and thiophene, respectively.

Alkenylfurans and Related Products

2-Vinylfuran

The best known of the alkenylfurans is 2-vinylfuran (2-furylethylene), the furan analog of styrene. For the most part it has been synthesized by decarboxylation of 3-(2-furyl)acrylic acid,[348, 349, 134, 23, 350, 351, 352, 353, 354, 354a] but has also been obtained from furfurylidenemalonic acid,[355] and by decomposition of β-2-furyl-β-propionolactone (p. 617) derived by condensation of furfural with ketene.[356, 357, 358]

[345] Terent'ev, Kazitsyna and Turovskaya, *Vestnik Moskov. Univ.*, **3**, 159 (1948); *C. A.*, **44**, 5862 (1950).

[346] Terent'ev, Kazitsyna and Suvorova, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*) **19**, 1951 (1949); *C. A.*, **44**, 1954 (1950).

[347] Hodgson and Davies, *J. Chem. Soc.*, **1939**, 806.

[348] Liebermann, *Ber.*, **27**, 283 (1894).

[349] Moureu, Dufraisse and Johnson, *Ann. chim.* (*10*), **7**, 13 (1927).

[350] Galimberti, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 351; *C. A.*, **37**, 3410 (1943).

[351] Koton, Votinova and Florinskii, *J. Applied Chem. U. S. S. R.*, **14**, 181 (1941); *C. A.*, **36**, 1604 (1942).

[352] Brubaker (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,341,016 (1944); *C. A.*, **38**, 4272 (1944).

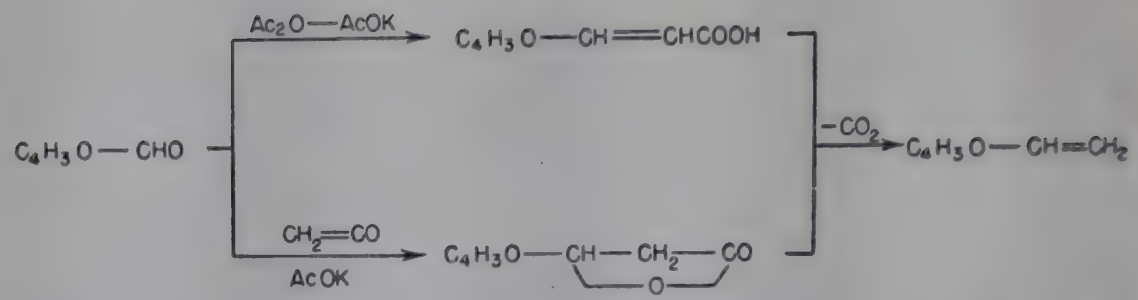
[353] Mora and Infiesta, *Combustibles Zaragoza*, **7**, 27 (1947); *C. A.*, **42**, 8519 (1948).

[354] Breault and Dermer, *Proc. Oklahoma Acad. Sci.*, **28**, 82 (1948); *C. A.*, **43**, 2615 (1949).

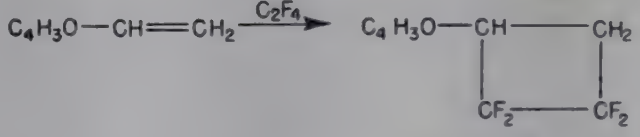
[354a] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 190 (1942); *C. A.*, **44**, 9721 (1950).

[355] Paul and Tchelitcheff, *Bull. soc. chim. France*, **1947**, 453.

[356] Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 275 (1933).



2-Vinylfuran is a colorless liquid, b.p. 94° (742 mm.), 99–100° (760 mm.); $d_4^{18.5}$ 0.9445; d_4^{25} 0.9316; $n_D^{18.5}$ 1.4992; n_D^{26} 1.4985. The surface tension is 29.8 dynes/cm. at 26°; viscosity, 5.35 millipoises at 26°.[354] For thermochemical data, see Landrieu, Baylocq and Johnson.[45] In air, the compound polymerizes rapidly, but it can be preserved indefinitely by addition of suitable antioxidants (hydroquinone, pyrogallol). It undergoes autoxidation more rapidly than styrene.[359] Aqueous potassium permanganate is reduced instantly[356]; bromine in carbon disulfide is absorbed rapidly.[348] For failure of an attempt to prepare vinylfuran oxide by the action of monoperoxyphthalic acid, see Breault and Dermer.[354] With tetrafluoroethylene at 150° for eight hours, addition takes place with formation of 3-(2-furyl)-1,1,2,2-tetrafluorocyclobutane, I (b.p. 86.5° (80 mm.); d_4^{25} 1.3341; n_D^{25} 1.4073) in 77 per cent yield.[360, 361]



I

As expected, a good portion of the published work with vinylfuran is concerned with its polymerization which has been effected with such agents as ozone, hydrogen peroxide, benzoyl peroxide, potassium perchlorate and potassium persulfate, among others. The polymer is said to be useful in coating compositions[362, 363, 364, 365, 353] (see also [351, 366, 367, 368, 368a]). Copoly-

[357] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,466,420 (1949); *C. A.*, **43**, 5037 (1948).

[358] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,469,110 (1949); *C. A.*, **43**, 5414 (1949).

[359] Moureu, Dufraisse and Johnson, *Bull. soc. chim.*, **43**, 586 (1928).

[360] Coffman, Barrick, Cramer and Raasch, *J. Am. Chem. Soc.*, **71**, 490 (1949).

[361] Barrick (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,462,345 (1949); *C. A.*, **43**, 4293 (1949).

[362] Imperial Chemical Industries Ltd., Brit. Pat. 349,442 (1929); *C. A.*, **26**, 2071 (1932).

[363] Sorensen (to E. I. du Pont de Nemours and Co.), U. S. Pat. 1,911,722 (1933); *C. A.*, **27**, 3952 (1933).

[364] Carpmael (to I. G. Farbenindustrie Akt.-Ges.), Brit. Pat. 487,604 (1938); *C. A.*, **33**, 283 (1939).

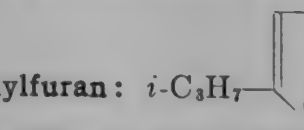
[365] Bock (to I. G. Farbenindustrie Akt.-Ges.), German Pat. 677,868 (1939); *C. A.*, **33**, 9496 (1939).

merization studies have been carried out with styrene,[369, 370, 371, 364] butadiene,[372, 371, 364] chloroprene,[373] acrylonitrile,[364] methacrylonitrile,[373] and with vegetable oils such as soya and linseed oils.[374]

Miscellaneous Alkenylfurans

2-(1-Propenyl)furan: [2-(2-methylvinyl)furan]; $C_4H_3O—CH=CHCH_3$; b.p. 132–133° (750 mm.); d_{15}^{14} 0.951; n_D^{14} 1.5115; obtained together with propylfuran and furylpropanone when ethylfurylcarbinol is passed over alumina at about 450°[148] (see also [375]).

2-Isopropenylfuran: [2-(1-methylvinyl)furan]; $C_4H_3O—C(CH_3)=CH_2$; b.p. 56–57° (75 mm.), 125–126° (atm.); d_{25}^{25} 0.9445; n_D^{25} 1.4966; by dehydration of dimethylfurylcarbinol.[376, 70] For copolymerization with butadiene, see Bachman and Heisey.[376]

5-Isopropyl-2-isopropenylfuran:  b.p. 66–68° (10 mm.); d_{25}^{25} 0.9020; n_D^{25} 1.4890; by dehydration of dimethyl-(5-isopropyl-2-furyl)carbinol.[376]

2-(2-Methyl-1-propenyl)furan: [2-(2,2-dimethylvinyl)furan]; $C_4H_3O—CH=C(CH_3)_2$; b.p. 153° (atm.); by condensation of furfural with isobutyric anhydride and potassium isobutyrate (or sodium acetate).[377, 378, 379]

2-(1-Butenyl)furan: [2-(2-ethylvinyl)furan]; $C_4H_3O—CH=CHC_2H_5$; b.p. 59–60°(24 mm.); d_{15}^{14} 0.932; n_D^{14} 1.5028; by passing *n*-propylfurylcarbinol over alumina at 450°.[140]

2-(1-Ethylvinyl)furan: Mixture of $C_4H_3O—C(C_2H_5)=CH_2$ and $C_4H_3O—C(CH_3)=CHCH_3$, obtained by refluxing methylethylfurylcarbinol with acetic anhydride. The mixture was reduced to 2-*sec*-butylfuran.[71]

2-(3-Methyl-1-butenyl)furan: [2-(2-isopropylvinyl)furan];

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[366] Kobeko, Mikhailov and Novikova, *J. Tech. Phys. U. S. S. R.*, **14**, 24 (1944) *C. A.*, **39**, 1569 (1945).

[367] Stewart (to The B. F. Goodrich Co.), U. S. Pat. 2,383,425 (1945); *C. A.*, **39**, 5545 (1945).

[368] Mighton (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,390,446 (1945); *C. A.*, **40**, 1688 (1946).

[368a] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 218 (1942); *C. A.*, **44**, 9721 (1950).

[369] Imoto, *J. Soc. Chem. Ind. Japan*, **45**, 1065 (1942); *C. A.* **42**, 6161 (1948).

[370] Bock (to General Aniline and Film Corp.), U. S. Pat. 2,442,283 (1948); C. A., **42**, 6165 (1948).

[371] I. G. Farbenindustrie Akt.-Ges., French Pat. 830,122 (1938); *C. A.*, **33**, 1417 (1939).

[372] Frank, Adams, Blegen, Smith, Juve, Schroeder and Goff, *Ind. Eng. Chem.*, **40**, 120 (1948).

[373] Clifford (to Wingfoot Corp.), U. S. Pat. 2,444,807 (1948); *C. A.*, **42**, 7106 (1948).

[374] Mighton (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,401,769 (1946); *C. A.*, **40**, 4898 (1946).

[375] Chelintzev, *Bull. soc. chim.* (**5**), **4**, 819 (1937).

[376] Bachman and Heisey, *J. Am. Chem. Soc.*, **71**, 1985 (1949).

[377] Baeyer and Tonnies, *Ber.*, **10**, 1364 (1877).

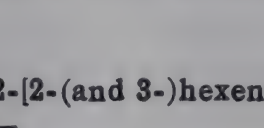
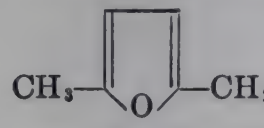
[378] Tonnies and Staub, *Ber.*, **17**, 850 (1884).

[379] Wagner (to Phillips Petroleum Co.), U. S. Pat. 2,431,216 (1947); *C. A.*, **42**, 1609 (1948).

C_4H_3O—CH=CHCH$(CH_3)_2$; b.p. 64–66° (13 mm.); 165–167° (atm.); by condensation of furfural with isovaleric anhydride and sodium isovalerate.[380, 379]

2-(1-Ethyl-1-propenyl)furan: C_4H_3O—$C(C_2H_5)$=$CHCH_3$; m.p. 249° (?); by dehydration of diethylfurylcarbinol.[381]

Hexenylfuran: b.p. 81–82° (24 mm.); n_D^{20} 1.4728; obtained in 46% yield together with dihexenylfuran (2 per cent) by reaction of furan and 2-methylpentadiene under the influence of boron fluoride.[62]

5-Methyl-2-[2-(and 3-)hexenyl]furan:  and  . A mixture of the two isomers, boiling in the range 80–95° (12.5 mm.), was obtained by dehydration of 1-(5-methyl-2-furyl)-3-hexanol.[382]

3-(4-Methyl-3-pentenyl)furan, II: (perillene); b.p. 93° (25 mm.), 185–186° (760 mm).; d_4^{20} 0.9017; n_D^{21} 1.4705. Natural product derived from *Perilla frutescens*[24] (see also [26]).

2-(2-Phenylvinyl)furan: C_4H_3O—CH=CHC_6H_5; m.p. 49–50°, 53–54°; obtained by dehydration of benzylfurylcarbinol,[86] and by decarboxylation of 2-phenyl-3-(2-furyl)acrylic acid.[304]

2-(2-Benzylvinyl)furan: [2-(3-phenyl-1-propenyl)furan]; C_4H_3O—CH=$CHCH_2C_6H_5$; b.p. 138–140° (10 mm.); d_{15}^{12} 1.046; n_D^{12} 1.5794; by distillation of phenethylfurylcarbinol at atmospheric pressure. Used for the synthesis of Carlina oxide.[20]

2-(3-Phenyl-2-propenyl)furan: C_4H_3O—CH_2CH=CHC_6H_5; b.p. 146.5–147° (13 mm.); d_4^{20} 1.029; n_D 1.552. This product, an isomer of the preceding compound, was also synthesized in connection with studies relating to the constitution of Carlina oxide. It was obtained by sodium and alcohol reduction of furfurylideneacetophenone to the corresponding carbinol, conversion of the latter to the chloride and removal of the elements of hydrogen chloride by heating with fused sodium acetate in glacial acetic acid.[22]

2-(1,2-Diphenylvinyl)furan: (α-2-furylstilbene); C_4H_3O—$C(C_6H_5)$=CHC_6H_5; b.p. 210–215° (15 mm.); formed by loss of the elements of water from benzylphenylfurylcarbinol when heated on a water bath with a large excess of formic acid.[383] While the compound resembles the estrogens in structure, it has little or no physiological activity. It is of some interest, however, since it is an estrogen antagonist.

2-(1-*p*-Xenyl-2-phenylvinyl)furan: C_4H_3O—$C(p$—$C_6H_5C_6H_4)$=CHC_6H_5; m.p. 87°; b.p. 285–300° (13 mm.); by the action of benzylmagnesium chloride on *p*-xenyl furyl ketone.[384]

Alkadienylfurans

2-(1,3-Butadienyl)furan: C_4H_3O—CH=CHCH=CH_2; no constants; in low yield from furfural and crotonic acid when these reagents are passed, in the vapor phase at 350°, through a tube containing potassium acetate on silica gel.[352] Also derived from furfurylideneacetone by reduction to the corresponding unsaturated alcohol

[380] Schaarschmidt, Georgeacopol and Herzenberg, *Ber.*, **51**, 1059 (1918).
[381] Hale, McNally and Pater, *Am. Chem. J.*, **35**, 68 (1906).
[382] Hunsdiecker and Wirth, *Ber.*, **75**, 460 (1942).
[383] Buu-Hoi and Hong-Ki-Wei, *Compt. rend.*, **220**, 175 (1945).
[384] Buu-Hoi, Nguyen-Hoan, Lecocq and de Clercq, *Rec. trav. chim.*, **67**, 795 (1948).

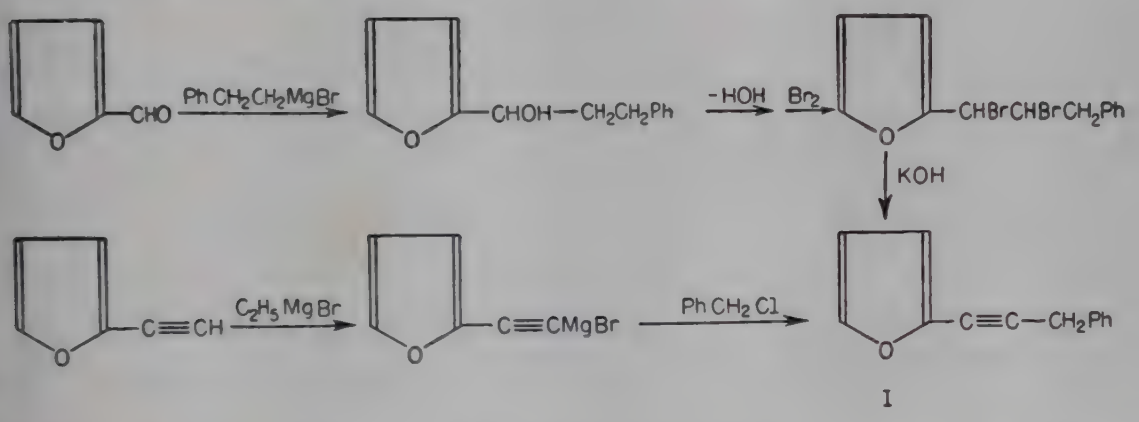
nd subsequent dehydration.[384a] For polymerization and copolymerization of this ompound and its homologs, see Bock[385, 386, 387] (see also [367]).

-(4-Methyl-1,4-pentadienyl)furan, III: (α-clausenan); b.p. 177° (684 mm.); d_{30}^{30} .9120; n_D^{30} 1.4752. This product was isolated from the oil obtained from the leaves f *Clausena willdenovii*.[29, 30, 31, 32]

Alkynylfurans

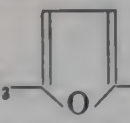
-Ethynylfuran: (2-furylacetylene); $C_4H_3O—C{\equiv}CH$; b.p. 105–106° (760 mm.); d_4^{20} .9919; n_D^{20} 1.5055; obtained by brominating 2-vinylfuran, and subsequently re- oving two molecular equivalents of hydrogen bromide by the action of alcoholic otassium hydroxide.[349, 23] The compound explodes on heating and when exposed to oncentrated nitric acid.

-(3-Phenyl-1-propynyl)furan: (benzyl-2-furylacetylene); (Carlina oxide); I (below); s a naturally occurring product from the roots of *Carlina acaulis*, b.p. 115–117°. mm.), 167–168° (20 mm.); d_{20} 1.0610; n_D^{20} 1.5810[21, 23] (see also [22, 19]). The synthetic roduct, b.p. 114–115° (1 mm.), 164–166° (20 mm.); d_{20} 1.0610, d_{15}^{17} 1.054; n_D^{20} 1.5875; n_D^{17} 1.573, was obtained by two separate routes as outlined below.[23, 20]



I

2-(3-Phenyl-2-propynyl)furan: (phenylfurfurylacetylene); $C_4H_3O—CH_2C{\equiv}CC_6H_5$; b.p. 160–161° (20 mm.); d_{17}^{17} 1.0683, d_4^{17} 1.0696; n_D^{17} 1.5833. This product, an isomer of I (above), was synthesized as part of the program of clearing up the constitution of Carlina oxide. It was obtained from phenylacetylenylmagnesium bromide by the action of furfuryl chloride.[19]

5-Methyl-2-(5-methyl-5-hexen-3-ynyl)furan: [6-(5-methyl-2-furyl)-2-methylhex-1-ene-3-yne];  $—CH_2CH_2C{\equiv}CC(CH_3){=}CH_2$; b.p. 107–109° (11 mm.); d_4^{20} 0.9856; n_D^{20} 1.5200. Obtained by interaction of 2-methylfuran and 2-methylhex-5-ene-3-yne-2-ol, $(CH_3)_2C(OH)C{\equiv}CCH{=}CH_2$, at about 120° in the presence of aqueous sulfur dioxide, and using pyrogallol as a polymerization inhibitor[309]; compare p.

[384a] Imoto and Hachihama, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 297 (1942); *C. A.*, **44**, 9722 (1950).

[385] Bock (to I. G. Farbenindustrie Akt.-Ges.), U. S. Pat. 2,194,416 (1940); *C. A.*, 34, 4839 (1940).

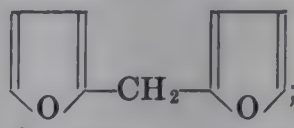
[386] Bock (to I. G. Farbenindustrie Akt.-Ges.), German Pat. 717,171 (1942); *C. A.*, 38, 2347 (1944).

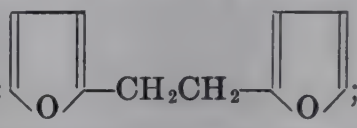
[387] I. G. Farbenindustrie Akt.-Ges., French Pat. 850,182 (1939); *C. A.*, **36**, 1701 (1942).

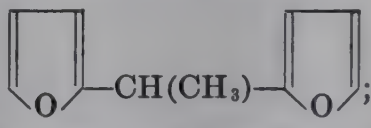
63 for similar condensations with acrolein, crotonaldehyde and the like. The product forms an adduct, m.p. 130°, with maleic anhydride.

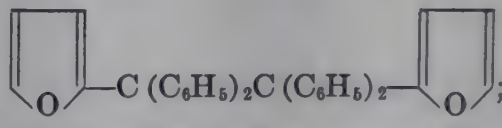
Compounds Containing Two Furan Nuclei

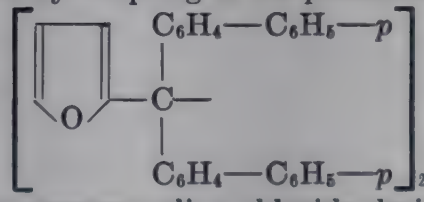
2,2′-Bifuryl: [2-(2-furyl)furan];  ; b.p. 63–64° (11 mm.); by decarboxylation of 2-(2-furyl)furan-3-carboxylic acid.[333, 178] For catalytic reduction to octahydrobifuryl, together with 1,8-octanediol, see Kondo, Suzuki and Takeda.[305]

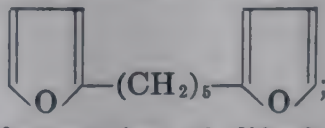
Di-2-furylmethane: (2-furfurylfuran);  ; m.p. *ca.* −30°; b.p. 78° (12 mm.), 80.5° (19.5 mm.); d_4^{20} 1.102; n_D^{20} 1.5049; by reduction of difuryl ketone and also, in low yield, by interaction of furylmagnesium bromide and furfuryl chloride[333, 254] (see also [388, 389]). It has also been found as a product during the acid-catalyzed resinification of furfuryl alcohol (p. 222).

sym.-**Difurylethane:**  ; b.p. 87–88° (12 mm.); prepared by reduction of (1) *sym.*-difurylethylene using sodium and alcohol, and (2) desoxyfuroin by the Wolff-Kizhner technique[74] (see also [390]).

1,1-Difurylethane:  ; b.p. 80° (10 mm.); n_D^{16} 1.5040; by saponification and subsequent decarboxylation of the condensation product of furoic ester and acetaldehyde in sulfuric acid[388] (see also [391]).

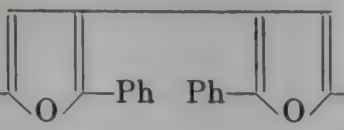
sym-**Tetraphenyldifurylethane:**  ; m.p. 149–150°; from diphenylfurylmethyl chloride by coupling in the presence of mercury.[84]

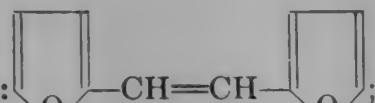
sym-**Tetra-*p*-xenyldifurylethane:**  ; m.p. 203–204°; as in preceding preparation from the corresponding chloride derivative.[84]

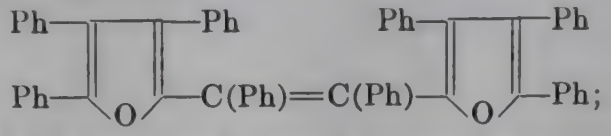
1,5-Di(2-furyl)pentane:  ; no constants. Reported as the product obtained on hydrogenation of difurfurylideneacetone over nickel in the presence of alkali.[392]

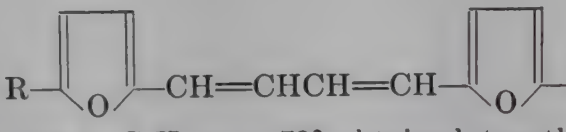
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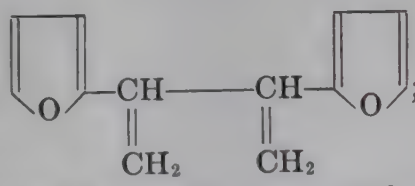
[388] Dinelli and Marini, *Gazz. chim. ital.*, **67**, 312 (1937); *C. A.*, **32**, 154 (1938).
[389] Marini, *Gazz. chim. ital.*, **69**, 340 (1939); *C. A.*, **33**, 8607 (1939).
[390] Fenton and Gostling, *J. Chem. Soc.*, **79**, 807 (1901).
[391] Dinelli and Marini-Bettolo, *Gazz. chim. ital.*, **71**, 117 (1941); *C. A.*, **36**, 1928 (1942).

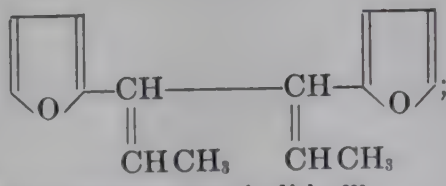
3,3′-Bis(2,5-diphenylfuran):  m.p. 195–196°; in good yield by ring closure of 1,2,3,4-tetrabenzoylbutane when heated in acetic anhydride containing a small amount of sulfuric acid.[113] It was also obtained as a by-product due to coupling of 3-bromo-2,5-diphenylfuran when treated with methylmagnesium iodide.[268]

***sym*-Difurylethylene:**  m.p. 98°, 100°, 101°; by pyrolysis of (1) polythiofurfural[393] (see also [394, 395]), and (2) furfuralazine.[396]

α,β-Bis(3,4,5-triphenyl-2-furyl)stilbene:  m.p. 233°; by the action of zinc on 3,4,5-triphenylfuryl phenyl ketone in acetic acid.[228]

1,4-Di(2-furyl)-1,3-butadienes:  no constants; R = CH_3, m.p. 108°; R = *i*—C_3H_7, m.p. 78°; obtained, together with the appropriate 2-R-4-hydroxycoumarone by condensation of furfural, 5-methylfurfural and 5-*i*-propylfurfural, respectively, with sodium succinate in acetic anhydride.[161] This work was primarily concerned with the synthesis of homologs of 4-hydroxycoumarone (see also [397, 398]).

2,3-Di(2-furyl)-1,3-butadiene:  m.p. 145°; by the action of methylmagnesium iodide on furil and subsequent decomposition by aqueous acid.[399]

3,4-Di(2-furyl)-2,4-hexadiene:  m.p. 128°; as in the preceding preparation using ethylmagnesium iodide.[399]

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[392] Cornubert and Phélisse, *Compt. rend.*, **229**, 460 (1949).
[393] Bruins, *J. Am. Chem. Soc.*, **51**, 1270 (1929); *Iowa State Coll. J. Sci.*, **10**, 51 (1935).
[394] Schwanert, *Ann.*, **134**, 61 (1865).
[395] Baumann and Fromm, *Ber.*, **24**, 3591 (1891).
[396] Pascal and Normand, *Bull. soc. chim.* (4) **9**, 1059 (1911).
[397] Kehrer and Kleberg, *Ber.*, **26**, 345 (1893).
[398] Fichter and Scheuermann, *Ber.*, **34**, 1626 (1901).
[399] Mironescu, Ioanid and Nicolescu, *Bul. soc. chim. România*, **14**, 187 (1932); *Chem. Centr.*, **1933**, II, 875.

Chapter 3

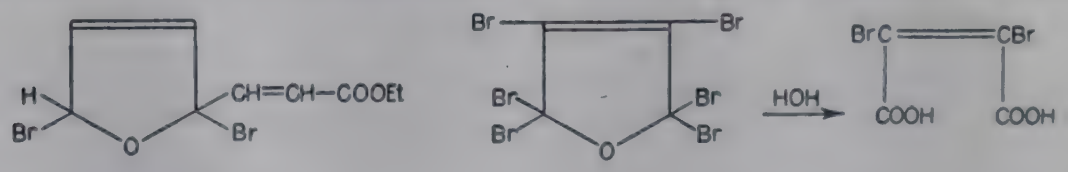
HALOGEN DERIVATIVES OF FURAN COMPOUNDS

This chapter includes all furan compounds possessing one or more halogen atoms attached directly to the nucleus, regardless of the mode of formation. Furans containing halogen solely on a side chain are treated elsewhere. For example, (haloaryl)furans are considered as arylfurans (Chapter 2); (haloalkyl)furans, as functional derivatives of the corresponding alcohols (Chapter 7). On the other hand, the behavior of all furan types on direct halogenation is discussed here, irrespective of whether reaction occurred on the nucleus, on a side chain, or both.

Introduction

As expected in view of the unsaturated nature of the furans, both addition and substitution products are obtainable by the action of chlorine and bromine. In a number of instances, di- and tetrahalo addition compounds have been successfully isolated by carrying out the reaction at low temperature in anhydrous medium.

The order of addition to the nucleus has been rather satisfactorily established. Experimental evidence is reasonably conclusive in demonstrating that the dihalo addition products possess the 2,5-dihydrofuran configuration. Gilman and Wright[1] favored this type of structure as that which best explained the properties of the dibromide, I,[a] obtained by the action of bromine on 3-(2-furyl)acrylic ester. It is also the most plausible configuration for the tetrabromofuran dibromide, II, isolated by Hill and Hartshorn,[3] in view of the fact that hydrolysis gives rise to dibromomaleic acid. The more recent work of Clauson-Kaas[4, 5] concerning the reaction of bromine



I II

[a] In a recent paper, Dann[2] formulates I as a 4,5-dibromo-4,5-dihydrofuran, based on light absorption data, and comparison with the bromine adducts of 2,4,6-octatrienoic ester.

[1] Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 3349 (1930).

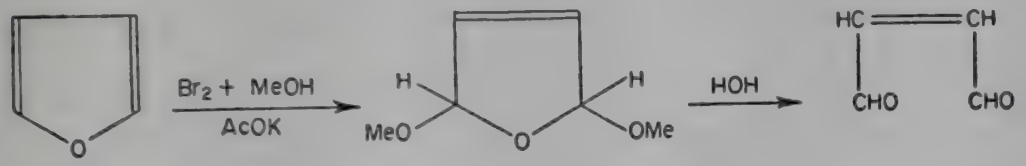
[2] Dann, *Chem. Ber.*, **80**, 435 (1947).

[3] Hill and Hartshorn, *Ber.*, **18**, 448 (1885).

[4] Clauson-Kaas, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd*, **24**, 18 pp. (1947); *C. A.*, **42**, 1930 (1948).

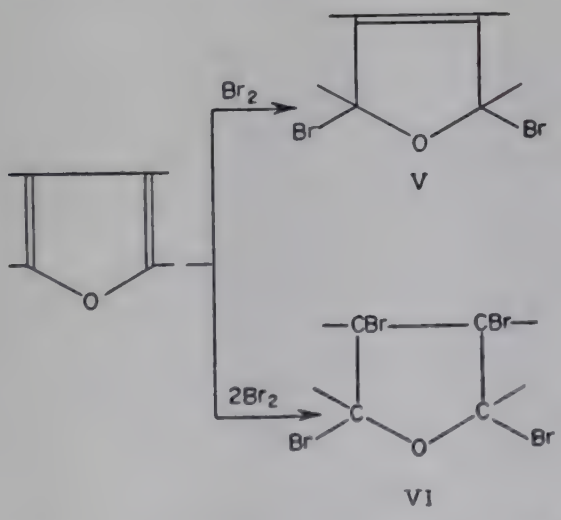
[5] Clauson-Kaas, *Acta Chem. Scand.*, **1**, 397 (1947).

with furan itself would appear to offer additional support in favor of a 1,4-type addition to the dienic system as the mechanism of the initial reaction, at least at low temperature. Because of the anticipated instability of the expected 2,5-dibromo-2,5-dihydrofuran, however, no attempt was made to isolate it as such. Instead, bromination was carried out at −10°, in methanol containing anhydrous potassium acetate, and 2,5-dimethoxy-2,5-dihydrofuran, III (see Chapter 2), was isolated in 47 per cent yield.[4] The structure of III, a cyclic acetal, was proven by its hydrolysis to malealdehyde, IV, and several identifying derivatives were prepared. In a similar manner, 2,5-diacetoxy-2,5-dihydrofuran was obtained by the action of bromine on furan in a mixture of glacial acetic acid and anhydrous potassium acetate.[5]



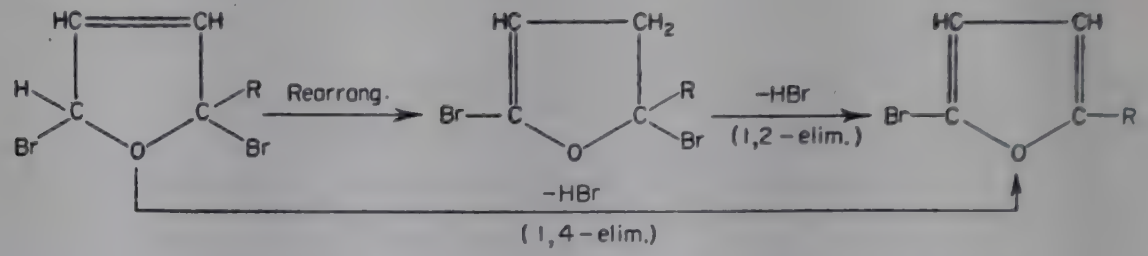
III IV

The formation of tetrahalide, VI, might be considered to go forward by the further action of halogen on the dihalide, V. On the other hand, the latter may not be intermediate in the formation of VI, which conceivably could be formed directly from furan types by a 1,2-type addition mechanism. No clarification of this point can be offered at this time.

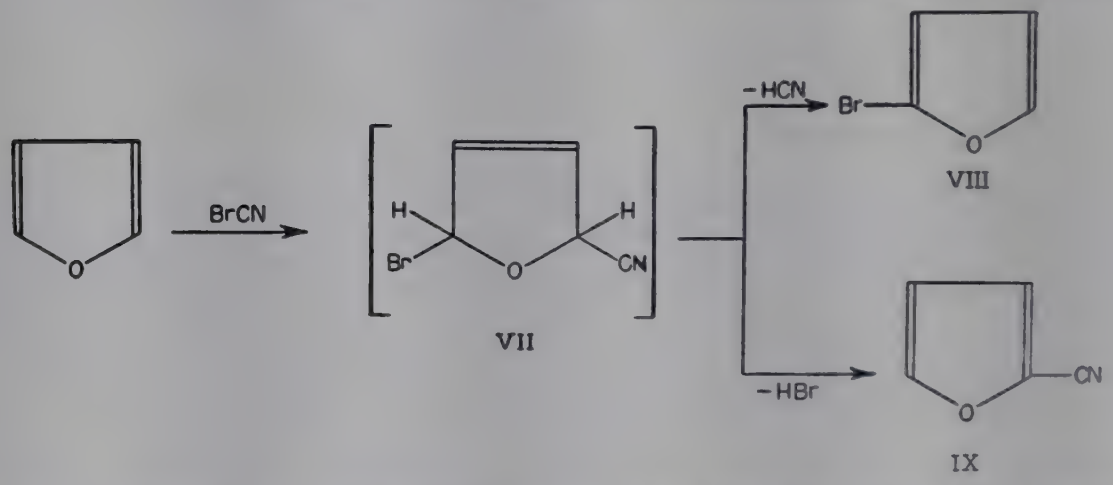


Where such a reaction is possible, compounds of type V and VI may undergo dehydrohalogenation rather readily to form halogen-substituted furans. Thus, Gilman and Wright[1] call attention to the spontaneous dehydrobromination of the dibromide, I, with formation of 3-(5-bromo-2-furyl)acrylic ester. This suggests a 1,4-type elimination of hydrogen bromide from the addition compound, although the possibility may not be excluded that elimination is preceded by a prototropic rearrangement as

illustrated below:



Related, is the work of Klopp and Wright[6] who isolated small quantities of both 2-bromofuran, VIII, and 2-furonitrile, IX, by the action of cyanogen bromide on furan. As pointed out by these investigators, this observation suggests preliminary formation of a 1,4-addition compound, VII (not isolated), followed by elimination of hydrogen cyanide or hydrogen bromide. However, it is interesting to note that when this same reaction was carried



out in dioxane, only bromofurans (VIII in 49 per cent yield together with some 2,5-dibromofuran) were obtained. No furonitrile could be detected among the products under these conditions. If the reaction does, in fact, go forward by way of VII, it is evident that the elimination step, in this instance, is confined to loss of hydrogen cyanide.

Other examples of the formation of halogen-substituted furans from intermediate addition compounds are given in the text which follows, and it has been suggested[1] that this represents the mechanism of substitution. Whether or not substitution is necessarily preceded by addition, however, can not be established from existing information. The possibility can not be excluded that addition and substitution may occur by separate routes, perhaps through a common intermediate on the basis of the indications obtained by Price in his work on the bromination of phenanthrene.[7] For example, reaction of chlorine with 2-furoic ester at 145° proceeds with liberation of hydrogen chloride. If the reaction is stopped when the gain in weight corresponds to the substitution of one equivalent of chlorine,

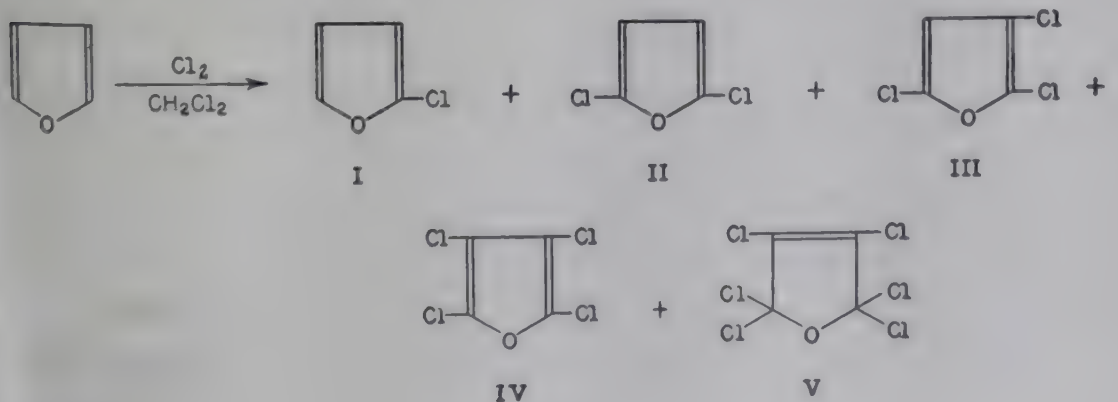
[6] Klopp and Wright, *J. Org. Chem.*, **4**, 142 (1939).
[7] Price, *J. Am. Chem. Soc.*, **58**, 2101 (1936); *Chem. Revs.*, **29**, 37 (1941).

ethyl 5-chloro-2-furoate is obtained as the major product.[8] This product might have been formed by direct substitution, by thermal dehydrohalogenation of an intermediate dihalide, or by a combination of these.

The great lability of the halogen atoms of the addition products obviously places limitations on the reaction media which may be employed in the halogenation of furan compounds. Facile alcoholysis and acylolysis with replacement of the bromine atoms by methoxyl and acetoxyl is clearly indicated by the work of Clauson-Kaas, from which the importance of avoiding moisture will be readily apparent. The solvents most commonly employed are carbon tetrachloride, chloroform and carbon disulfide. In several instances, halogenation has been carried out directly with no added solvent.

Derivatives of Furan

The known halogen substituted derivatives of furan have been prepared almost exclusively by indirect means. As a matter of fact, prior to the recent patent disclosure of Cass and Copelin[9] (see also [10]) no work had been reported on the action of chlorine on furan. Henninger[11] had attempted direct bromination in carbon tetrachloride at $-5°$, and in this way obtained two products which he believed to be a monobromo- and a dibromofuran. Only the latter was described, however, and the physical constants are not in good agreement with authentic 2,5-dibromofuran obtained by indirect synthesis.[3] In the chlorination work, Cass and Copelin employed yet lower temperatures (*ca.* $-40°$) in order to minimize resinification due to liberated hydrogen chloride. Under these conditions, using methylene chloride as a solvent and slowly introducing 1.6 moles of chlorine per mole of furan, they obtained a mixture of 2-chloro- (I), 2,5-dichloro- (II), and 2,3,5-trichlorofuran (III) in the proportion 9:4:1. By reducing the amount of chlorine, the proportion of I in the product mixture is increased; the relative quantities of II and III are increased by increasing the ratio of chlorine to furan. When this ratio is 3:1 or greater, yet more highly chlorinated furans are formed as by-products, including tetrachlorofuran, IV, and its dichloride, V, the latter as a mixture of two crystalline forms melting at 18° and



39–40°, respectively. Vapor-phase chlorination of furan to 2-chlorofuran is described in a subsequent disclosure[12] by the same investigators.

Of the indirect procedures for introducing a halogen atom into furan, that using cyanogen bromide has already been mentioned (p. 82). Other compounds containing active bromine, such as N-bromosuccinimide and N-bromophthalimide, have not been employed with furan itself, but in view of the behavior of the former with naphthalene and thionaphthene, it is not unlikely that it could be used for the bromination of furan.[13]

Decarboxylation of the appropriate halofuroic acids has proved to be a useful procedure for obtaining the simple halofurans.[14, 15, 16] Copper-bronze or finely divided nickel act to catalyze the decarboxylation, and detrimental side-reactions may be minimized by carrying out the decomposition in the presence of a basic material such as quinoline.[15]

$$2,5\text{—}C_4H_2O\text{—}(Cl)(COOH) \xrightarrow[\text{(Cu—bronze; quinoline)}]{\text{heat}} C_4H_3O\text{—}Cl + CO_2$$

The halofurans may also be synthesized from furan compounds possessing more or less easily replaceable substituents. Thus, in several instances, the carboxyl group of α-furoic acids has been replaced by halogen. For example, 2-iodofuran may be obtained by refluxing an aqueous, alkaline solution of 2-furoic acid with iodine and potassium iodide,[17] and 2,5-diiodofuran is formed in like manner from 2,5-furandicarboxylic acid.[18] Similarly, treatment of 5-bromo-2-furoic acid in aqueous alkali with slightly more than one mole of bromine gives 2,5-dibromofuran.[3]

$$Br\text{—}C_4H_2O\text{—}COOH \xrightarrow[KOH]{Br_2} Br\text{—}C_4H_2O\text{—}Br$$

In common with the behavior of other organic mercurials, the carbon-metal bond of furylmercuric chlorides and acetates is likewise ruptured by the action of halogens with the formation of halofurans. In this way, Gilman and Wright[19] obtained 2-iodo-, 2,5-diiodo-, and 2,3,4,5-tetraiodofuran

[8] Hill and Jackson, *Ber.*, **20**, 252 (1887).

[9] Cass and Copelin (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,430,667 (1947); *C. A.*, **42**, 2284 (1948).

[10] E. I. du Pont de Nemours & Co., Brit. Pat. 611,851 (1948); *C. A.*, **43**, 3041 (1949).

[11] Henninger, *Ann. chim. phys.* (*6*), **7**, 209 (1886).

[12] Cass and Copelin (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,443,493 (1948); *C. A.*, **42**, 7340 (1948).

[13] Buu-Hoi and Lecocq, *Compt. rend.*, **222**, 1441 (1946).

[14] Canzoneri and Oliveri, *Gazz. chim. ital.*, **17**, 42 (1887).

[15] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).

[16] Whittaker, *Rec. trav. chim.*, **52**, 352 (1933).

[17] Gilman, Mallory and Wright, *J. Am. Chem. Soc.*, **54**, 733 (1932).

[18] Phelps and Hale, *Am. Chem. J.*, **25**, 445 (1901).

[19] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

by the action of aqueous iodine and potassium iodide on the mixture of furylmercuric chlorides obtained by mercuration of furan. No triiodofuran

$$C_4H_3O—HgCl \xrightarrow{I_2—KI} C_4H_3O—I$$

was found in the reaction mixture. 3-Furylmercuric chloride behaves similarly, although the conversion to 3-iodofuran proceeds much more slowly.[19]

Treatment of 2-furylmercuric chloride, in non-aqueous medium, with sulfuryl chloride or bromine, gives rise to 2-chloro- or 2-bromofuran in low yield.[19] These same products are also formed by the action of cupric chloride and cupric bromide, respectively, on 2-furanboronic acid.[20]

The monohalogen substituted derivatives of furan are colorless liquids of sweet odor; sparingly soluble in water, but readily soluble in alcohol, ether and benzene. On storage they discolor and slowly resinify. As is frequently true with furan types, they should be stored out of contact with air (oxygen) to avoid autoxidation. Phenolic type antioxidants, such as hydroquinone, act as stabilizers in normal storage. Long contact with aqueous mineral acids results in complete resinification.

The behavior of the halofurans in the diene synthesis is discussed elsewhere (Chapter 2). For dipole moment data, see Nazarova and Syrkin.[21] For the action of 2-bromofuran as a larvicide, see Bishopp *et al.*[22]

The bond between the halogen atom and the furan nucleus is quite stable, the halogens being rather surprisingly unreactive. Reagents such as aqueous sodium hydroxide and sodium cyanide, or metallic sodium, dimethylmercury and dimethylzinc are without action.[15]

Ordinary or activated magnesium fails to give the expected Grignard with 2-bromofuran[15]; a highly activated magnesium-copper alloy is required to induce reaction.[33] On the other hand, 2-iodofuran is sufficiently reactive to give a high yield of 2-furylmagnesium iodide with ordinary magnesium.[17] The Grignard reagent so obtained behaves normally with no indicated

[20] Johnson, Van Campen and Grummitt, *J. Am. Chem. Soc.*, **60**, 111 (1938).
[21] Nazarova and Syrkin, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk*, **1949**, 35; *C. A.* **43**, 4913 (1949).
[22] Bishopp, Cook, Parman and Laake, *J. Econ. Entomol.*, **16**, 222 (1923).
[23] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).
[24] Nazarova and Syrkin, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **19**, 777 (1949); *C. A.*, **44**, 1092 (1950).
[25] Canzoneri and Oliveri, *Gazz. chim. ital.*, **15**, 113 (1885).
[26] Hill and Sanger, *Proc. Am. Acad. Arts Sci.*, **21**, 135 (1885); *Ann.*, **232**, 46 (1886).
[27] Hill, *Ber.*, **16**, 1130 (1883).
[28] Hill and Cornelison, *Am. Chem. J.*, **16**, 188 (1894).
[29] Torrey, *Am. Chem. J.*, **19**, 668 (1897).
[30] Ciusa, *Gazz. chim. ital.*, **52**, II, 130 (1922); *C. A.*, **17**, 1466 (1923); *Ibid.*, **55**, 385 (1925); *C. A.*, **20**, 736 (1926).
[31] Ciusa and Grilla, *Gazz. chim. ital.*, **57**, 323 (1927); *C. A.*, **21**, 2686 (1927).
[32] Hill and Jackson, *Am. Chem. J.*, **12**, 112 (1890).
[33] Gilman, Peterson and Schulze, *Rec. trav. chim.*, **47**, 19 (1928).

TABLE 1. HALOGEN-SUBSTITUTED DERIVATIVES OF FURAN

Compound	Physical constants (°C.)	Ref.
Chlorofurans		
2-Chloro	b.p. 77.2–77.5 (744 mm.) d_{25} 1.189	15, 23, 9, 12
3-Chloro	b.p. 79.0–79.4 (742 mm.)	15, 23
2,5-Dichloro	b.p. 115 d_{25} 1.371	9, 10
3,4-Dichloro	m.p..3.8–4.0 b.p. 122.8–123.1 (744 mm.)	15
2,3,4-Trichloro	b.p. 151.7–152.7 (734 mm.)	15
2,3,5-Trichloro	b.p. 147 d_{25} 1.50	9, 10
2,3,4,5-Tetrachloro	m.p. 46–48 b.p. 107–108 (15 mm.)	9, 10
Bromofurans		
2-Bromo	b.p. 101.9–102.2 (744 mm.)	15, 23, 6, 16
3-Bromo	b.p. 102.5–102.6 (745 mm.)	15, 23, 14
2,5-Dibromo	m.p..5, 9–10 b.p. 51–52 (12 mm.), 164–165 (764 mm.)	3, 6, 11
2,3-Dibromo	b.p. 166.3 (744 mm.) d_{25}^{25} 1.9997; n_D^{25} 1.5458	24
3,4(?)-Dibromo	b.p. 165–167	25
2,3,4-Tribromo	b.p. 96–98 (20 mm.)	26
2,3,4,5-Tetrabromo	m.p. 64–65	27, 26, 28, 29, 18
Iodofurans		
2-Iodo	b.p. 43–45 (15 mm.)	17
3-Iodo	b.p. 43 (14 mm.), 132.2 (732 mm.)	19
2,5-Diiodo	m.p. 47	18
2,3,4,5-Tetraiodo	m.p. 145, 165	30, 31
Mixed		
2,3,4-Trichloro-5-bromo	m.p. 75–76	32

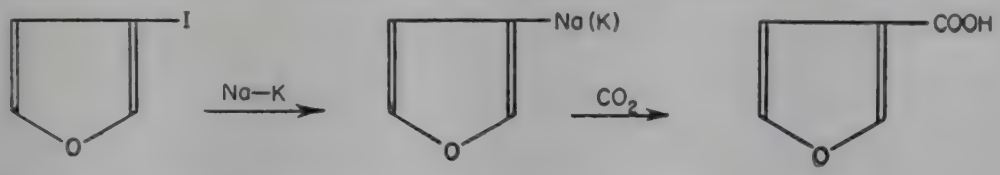
rearrangement; treatment with formaldehyde, ethyl chlorocarbonate, and ethyl orthoformate gives furfuryl alcohol, ethyl 2-furoate and furfural ethyl acetal, respectively.[34]

$$C_4H_3O\text{—}I \xrightarrow{Mg} C_4H_3O\text{—}MgI \xrightarrow{CH(OEt)_3} C_4H_3O\text{—}CH(OEt)_2$$

Unlike that in the α-isomer, the C-I linkage in 3-iodofuran is very resistant to cleavage. For example, this furan is recovered unchanged after heating with magnesium at 150° for sixteen hours.[19] It also fails to react

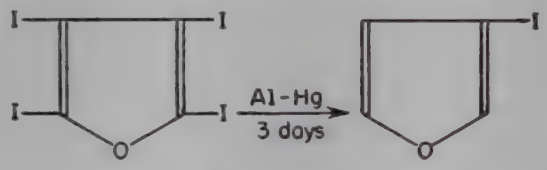
[34] Gilman and Franz, *Rec. trav. chim.*, **51**, 991 (1932).

with lithium in ether, and is attacked only very slowly by sodium-potassium alloy even at elevated temperatures. Exposure to this alloy for twenty-four hours at 115°, leaves 75 per cent of the halide unchanged and recoverable by distillation, leaving a residue which, on carbonation, gives rise to a small quantity of 3-furoic acid. This reaction has been cited as evidence for the intermediate formation of organometallic compounds in the Wurtz-Fittig reaction.[35] In view of the behavior of 2,4,5-triphenyl-3-bromofuran (p. 97) it is possible that treatment of 3-iodofuran with *n*-butyllithium would

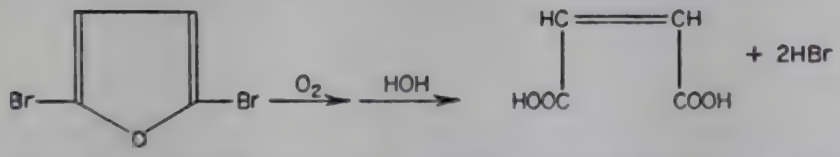


effect halogen-metal interconversion more smoothly.

Attempted reduction of 3-iodofuran further illustrates the relative inertness of the β-halogen atom. Exposure to aluminum amalgam for one week failed to dislodge the iodine atom, although this reagent is effective in stripping three of the four halogen atoms from tetraiodofuran.[19]



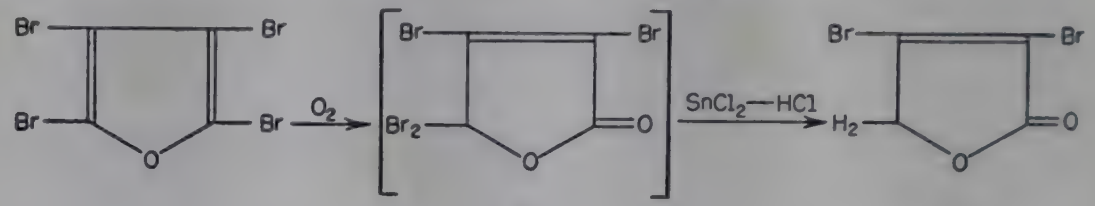
The halofurans are readily oxidized, and under aqueous conditions, the ring is ruptured with the formation of maleic or fumaric acids or halogenated derivatives of these acids. Thus, 2,5-dibromofuran is slowly attacked by atmospheric oxygen to give an oil which, on further aeration in aqueous solution, gives maleic acid and hydrobromic acid.[3] A similar oxidation of



tetrabromofuran was observed by Torrey[29] who exposed the dry product to pure oxygen in the sunlight. He measured the consumption of oxygen and observed the rate of uptake to be very slow after absorption of approximately 0.4–0.5 mole per mole of the halofuran. A reddish colored oil was obtained, which solidified on standing. Steam distillation gave a small quantity of the original bromo compound, and a residual liquor in which dibromomaleic and hydrobromic acids were identified. Reduction with stannous chloride gave rise to α,β-dibromo-γ-crotonolactone, VII, described earlier by Hill and Cornelison.[28] On the basis of these results, Torrey concluded that the main product of the addition of oxygen to

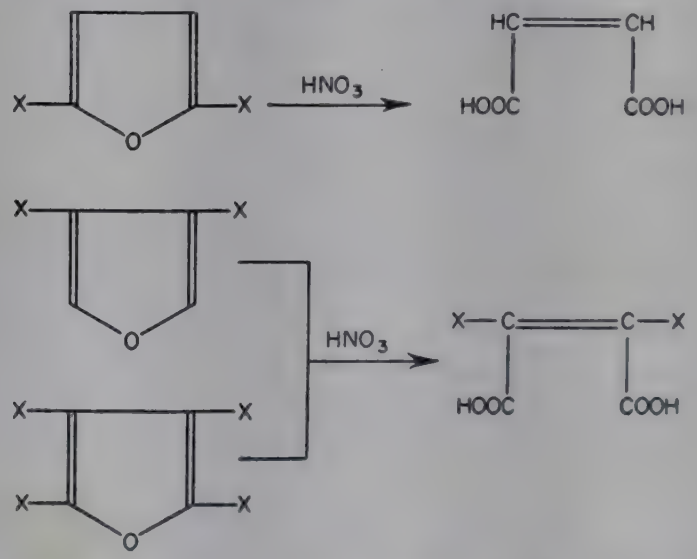
[35] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 2893 (1933).

tetrabromofuran is dibromomaleyl bromide (unsymmetrical form, VI; see Hill and Cornelison[28]). This may have resulted by rearrangement of an intermediate peroxide or ozonide of the form suggested by Schenck[36] as a result of his studies of the autoxidation of simple furans.



VI VII

Oxidation of 2,5-dibromofuran with nitric acid also gives maleic or fumaric acids depending upon the conditions of reaction.[3, 6] Tetrabromofuran behaves similarly giving dibromomaleic acid.[3] In like manner, dichloromaleic acid is obtained from 3,4-dichlorofuran, which under less strenuous oxidizing conditions is transformed into α,β-dichloro-β-formylacrylic acid (OHC—CCl=CCl—COOH), the so-called mucochloric acid.[15] Similar results are obtained using aqueous bromine as the oxidizing agent.

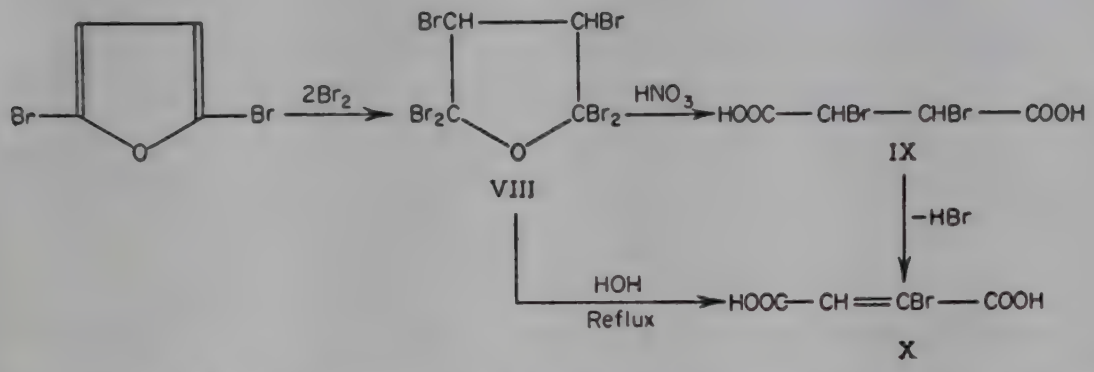


It will be noted that the oxidation reaction differentiates between alpha and beta halogen atoms in the original compound; those occupying an alpha position in the nucleus are removed, whereas beta halogens are retained in the oxidation product. This characteristic is of limited utility, however, since furan types possessing a single β-halogen substituent would give rise to the same oxidation product (a monohalomaleic acid) regardless of whether the halogen occupied position 3 or 4 in the original substituted furan. Thus, the oxidation method would not be serviceable to distinguish between 2,3- and 2,4-dihalofurans.

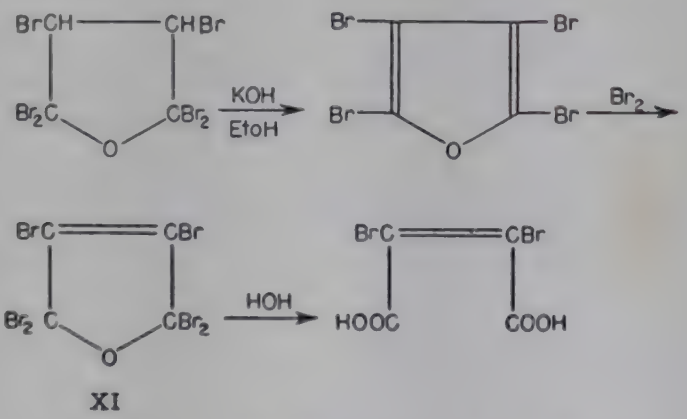
Treatment of halofurans with chlorine and bromine in non-aqueous medium has been carried out, in several instances, with the successful isolation of

[36] Schenck, *Naturwissenschaften*, **31**, 387 (1943); *C. A.*, **38**, 2336 (1944).

di- and tetrahalogen addition products. For example, 2,5-dibromofuran adds bromine to form dibromofuran tetrabromide, VIII (m.p. 110–111°; 112°),[3] which is also obtainable by the action of bromine on 2,5-diiodofuran.[18] With fuming nitric acid, VIII is converted into dibromosuccinic acid, IX, whereas boiling with water for an extended period results in the loss of five atoms of bromine to give a mixture of bromomaleic and bromofumaric acids, X.[3] Possibly the latter reaction proceeds by way of preliminary hydrolysis to dibromosuccinic acid, followed by loss of hydrogen bromide (see [37]).



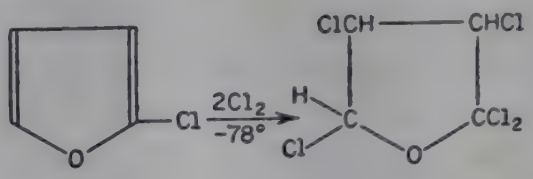
Elimination of two molecules of hydrogen bromide from 2,5-dibromofuran tetrabromide by the action of alcoholic potassium hydroxide gives rise to tetrabromofuran.[27, 29, 18] Treatment of the latter with dry bromine gives a dibromide, C_4Br_6O (m.p. 122–123°), which decomposes in aqueous medium to dibromomaleic acid. While no structure was assigned to the dibromide, the configuration shown below (XI) is in accord with the hydrolytic reaction cited.



By the action of chlorine on 2-chlorofuran in chloroform at −78° there is formed 2-chlorofuran tetrachloride, XII, a pale yellow, oily liquid (d_4^{25} 1.620) of penetrating odor.[38] Like VIII, this compound readily undergoes dehydrohalogenation on treatment with alcoholic caustic potash. With aqueous silver nitrate it undergoes a stepwise loss of chlorine as silver

[37] Lossen and Riebensahm, *Ann.*, **292**, 295 (1896); Lossen, *Ibid.*, **300**, 1 (1898).
[38] Lowe and Hamilton, *J. Am. Chem. Soc.*, **57**, 2314 (1935).

chloride, the extent of loss being influenced by temperature and by the acidity of the medium.



XII

Derivatives of Furan Homologs

In this section we shall consider the halogenation of those furan compounds which are substituted by one or more hydrocarbon residues, and describe the derivatives of this classification which possess one or more halogen atoms directly attached to the furan nucleus. Compounds of this general type, in which one or more hydrogen atoms of the hydrocarbon substituent have been replaced by halogen are also included.

Alkylhalofurans

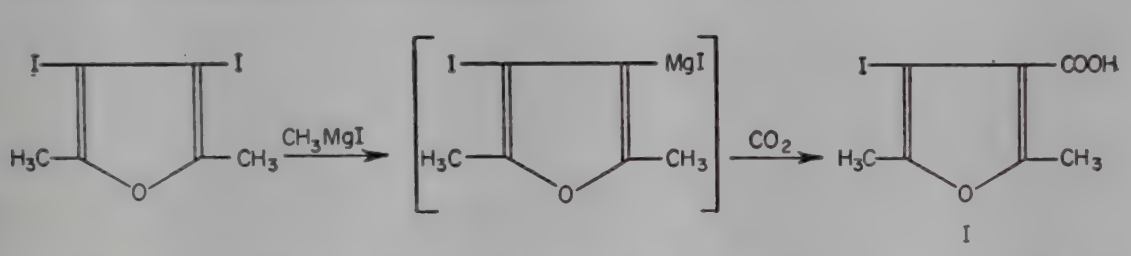
The comparatively few alkylhalofurans which have been reported were synthesized by indirect means as indicated in Table 2. Doubtless, the known sensitivity of the alkylfurans toward acidic reagents has discouraged attempts to introduce a nuclear halogen atom directly. Thus, there is no reported work on the action of halogens, the phosphorus halides, or thionyl or sulfuryl chlorides on the simple homologs of furan. As expected, N-bromosuccinimide attacks the side chain to form furylalkyl bromides[13] (see also Chapter 7).

Table 2. Alkylhalofurans

Substituted furan	Physical constants (°C.)	Source	Ref.
5-Chloro-2-methyl	b.p. 108–110 (740 mm.) d_4^{20} 1.1184 n_D^{20} 1.4611, 1.4619	(a) 5-chloro-2-methyl-3-furoic acid; (b) 5-chlorofurfural	39, 40
5-Iodo-2-methyl	b.p. 59 (18 mm.) d_4^{20} 1.861 n_D^{20} 1.5571	5-methyl-2-furylmercuric chloride	19
3(or 4)-Iodo-2-methyl	b.p. 57 (28 mm.) d_4^{20} 1.860 n_D^{20} 1.5489	diiodo-2-methylfuran	19
3-Iodo-2,5-dimethyl	b.p. 85.5–86 (20 mm.) d_4^{20} 1.699 $n_D^{22.6}$ 1.5388	2,5-dimethyl-3-furylmercuric chloride	41
3,4-Diiodo-2,5-dimethyl	m.p. 60.8	2,5-dimethyl-3,4-furanbis(mercuric chloride)	41

[39] Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).
[40] Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).
[41] Hurd and Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

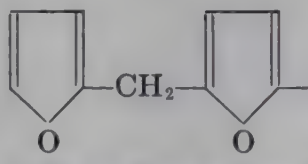
Gilman and his students found indications that alkyl groups tend to labilize furan nuclear halogen atoms. Thus, they compare the extremely inert β-iodine atom of 3-iodofuran (see p. 86) with that of 3-iodo-2,5-dimethylfuran,[b] the latter compound readily forming the corresponding organomagnesium iodide.[43, 34] 3,4-Diiodo-2,5-dimethylfuran, however, could not be brought into reaction with magnesium, even when heated in butyl ether up to 140°, nor by use of a special magnesium alloy.[41] In this instance, the iodine atoms were also found to be inert to potassium cyanide when an attempt was made to form the nitrile. Treatment with methylmagnesium iodide, did, however, effect a Grignard exchange reaction to a limited extent as evidenced by isolation of 2,5-dimethyl-4-iodo-3-furoic acid, I, on subsequent carbonation.[41]



I

5-Chloro-2-methylfuran does not react with ordinary, or activated magnesium in ether. It does react vigorously with metallic sodium but the products have not been investigated.[40]

The alkyliodofurans decompose in a matter of a few weeks storage, but are reasonably stable in solution.[41] 5-Chloro-2-methylfuran may be kept for six months, or more, under alkaline hydroquinone.[39]

5-Furfuryl-2-iodofuran: 

; b.p. 123° (9 mm.), n_D^{20} 1.5843.

Obtained in 70 per cent yield by the action of aqueous iodine-potassium iodide on 5-furfuryl-2-furylmercuric chloride. It does not react with magnesium, nor with silver nitrate.[13]

Arylhalofurans

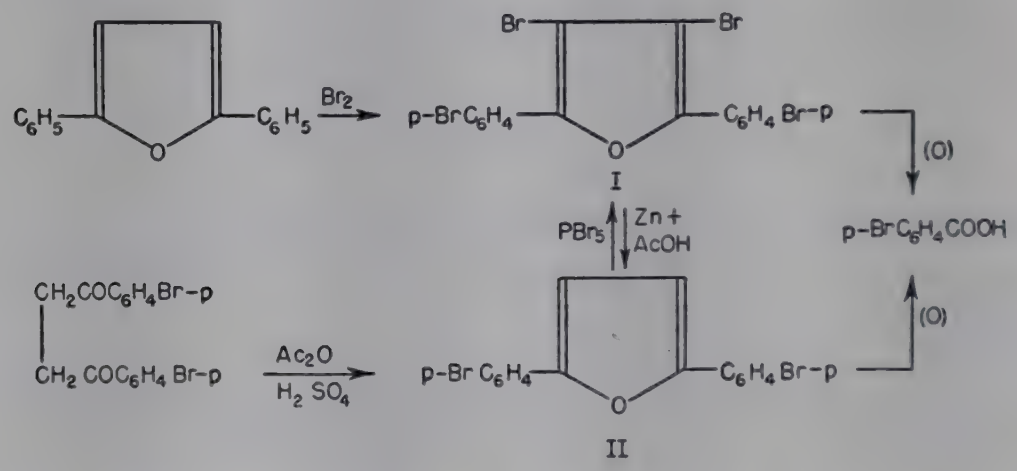
The introduction of halogens into 2,5-diarylfurans has been accomplished directly using bromine or phosphorus pentahalides. The initial attack by these reagents occurs at the beta positions of the furan nucleus, showing that these are more susceptible to halogenation than the unsubstituted positions of the aryl nuclei (phenyl and mesityl). The latter, however, may be halogenated subsequently if conditions permit.

[b] An attempt to synthesize bifuryl types from the halofuran using the copper coupling method resulted in failure.[42]

[42] Brown, *Iowa State Coll. J. Sci.*, **12**, 111 (1937).

[13] Gilman, Burtner and Wright, *J. Am. Chem. Soc.*, **54**, 1696 (1932).

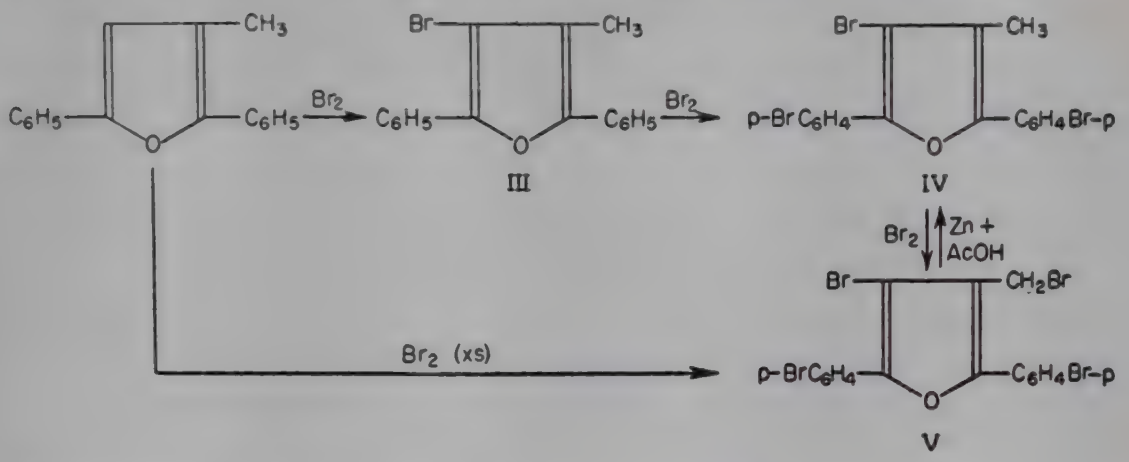
Perkin and Schloesser[44] obtained a tetrabromo substitution product by working up the reaction mixture resulting from the prolonged action of dry bromine on 2,5-diphenylfuran at room temperature. Later, Thiele and Rössner[45] isolated the same product by similar treatment of 2,5-diphenyl-2,5-dihydrofuran, and assigned to it the structure of 2,5-bis(*p*-bromophenyl)-3,4-dibromofuran, I, the correctness of which is established by the following reactions. Oxidation with chromic acid gives two equivalents of *p*-bromobenzoic acid.[45] Reduction with zinc and acetic acid removes two of the four bromine atoms with the formation of 2,5-bis(*p*-bromophenyl)-furan, II,[45] the structure of which is known by its synthesis from 1,4-bis(*p*-bromophenyl)-1,4-butanedione.[46] II likewise gives *p*-bromobenzoic acid on oxidation,[45] and is converted into I when placed in reaction with phosphorus pentabromide.[46]



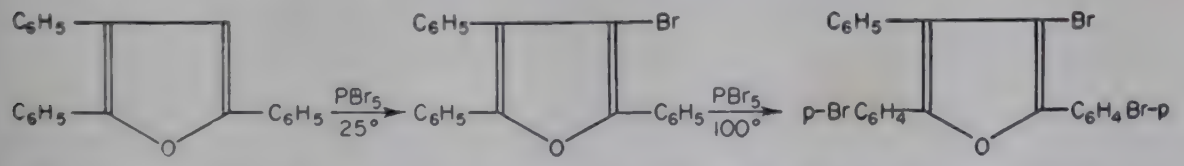
Reaction of bromine with 2,5-dimesitylfuran in carbon tetrachloride gives rise to a mixture of products from which some 2,5-dimesityl-3,4-dibromofuran may be isolated[47, 48] (see also [49]). Similarly, a difficultly separable mixture is obtained by treatment of 2,5-diphenyl-3-methylfuran with three moles of bromine in chloroform[50, 51], reaction occurring stepwise with the formation of mono- (III), tri- (IV) and tetrabromo (V) derivatives. Location of the bromine atoms in these compounds, and the order of bromination was deduced in the following manner. Only V could be reduced with zinc dust in acetic acid, one bromine being removed with formation of IV. The removable bromine atom must, therefore, have been the last to be

[44] Perkin and Schloesser, *J. Chem. Soc.*, **57**, 944 (1890).
[45] Thiele and Rössner, *Ann.*, **306**, 201 (1899).
[46] Lutz and Eisner, *J. Am. Chem. Soc.*, **56**, 2698 (1934).
[47] Lutz, Johnson and Wood, *J. Am. Chem. Soc.*, **60**, 716 (1938).
[48] Lutz and Kibler, *J. Am. Chem. Soc.*, **62**, 1520 (1940).
[49] Lutz and Reveley, *J. Am. Chem. Soc.*, **63**, 3180 (1941).
[50] Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2583 (1942).
[51] Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2585 (1942).

introduced, and it was assigned to the methyl group.[c] Oxidation of IV gave more than one mole of *p*-bromobenzoic acid indicating the presence of two *p*-bromophenyl groups. The fourth bromine atom, evidently the first to be introduced, was shown to be attached at the 4-position of the furan nucleus, since oxidation of III with nitric acid gave rise to the unsaturated diketone, $C_6H_5COC(CH_3)=CBr—COC_6H_5$. By employing slightly more than four moles of bromine, the tetrabromo substitution product, V, was obtained in 75 per cent yield from the original diphenylmethylfuran.[50, 51]



Halogenation of a number of arylfurans using phosphorus pentahalides was studied by Lutz and his associates. For example, 2,3,5-triphenylfuran reacts readily with phosphorus pentachloride at 100° with introduction of a chlorine atom at the unoccupied beta position of the furan nucleus.[52] With phosphorus pentabromide, under like conditions, the alpha phenyl substituents (but not the beta) are also attacked; in this way 2,5-bis(*p*-bromophenyl)-4-phenyl-3-bromofuran is obtained.[52] At lower temperature (25°), however, only the furan nucleus is brominated.



Similar results have been observed with 2,5-diphenylfuran which has two available beta positions. Reaction with phosphorus pentachloride gives rise to monochloro- (VI), or dichlorodiphenylfuran (VII) depending on the experimental conditions.[53, 54]. Thionyl chloride is ineffective, whereas

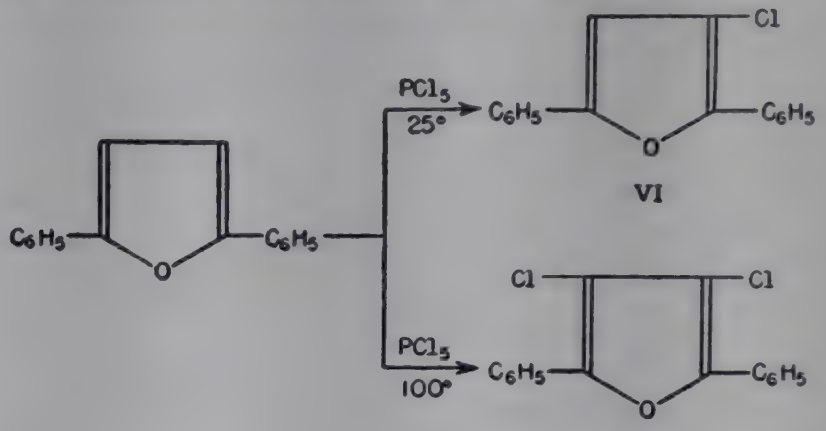
[c] Throughout Lutz' work, only aliphatic bromine atoms were found to be removed by the action of zinc and acetic acid. This is in contrast to the results reported by Thiele and Rössner when working with 2,5-bis(*p*-bromophenyl)-3,4-dibromofuran (see p. 98).

[52] Lutz, Tyson, Sanders and Fink, *J. Am. Chem. Soc.*, **56**, 2679 (1934).

[53] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 1193 (1934).

[54] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 2145 (1934).

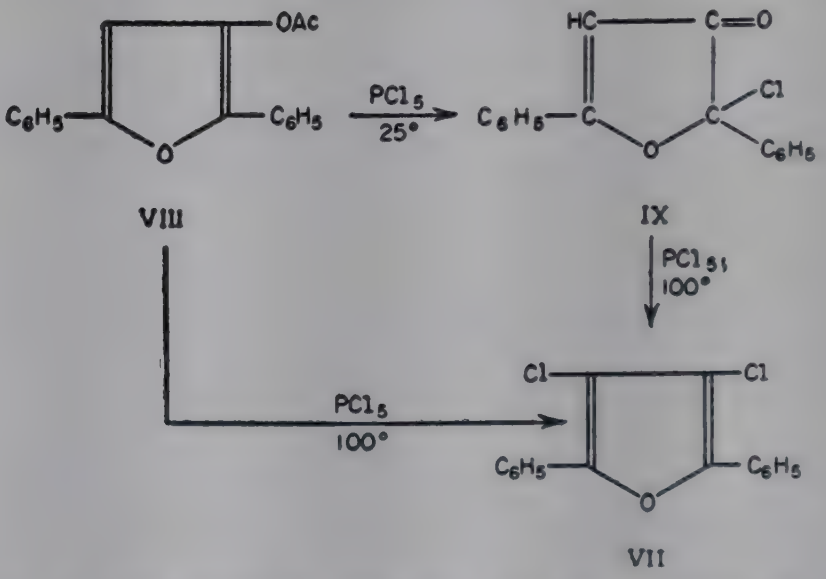
phosphorus pentabromide again introduced bromine once into each phenyl group besides brominating the furan ring[54] (see also [55, 56, 48]).



VI

VII

The action of phosphorus pentachloride on 2,5-diphenyl-3-furanol acetate (VIII) at 100° likewise leads to the formation of VII.[57] When the reaction is carried out at 25°, however, the first product obtained is the chlorofuranone, IX,[d] which then reacts further with the reagent at more elevated temperatures to give 2,5-diphenyl-3,4-dichlorofuran, VII.

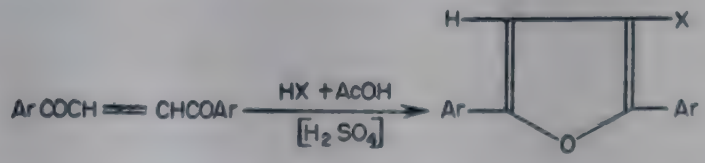


VIII

IX

VII

In addition to the foregoing methods for the preparation of arylhalofurans, many of these products have been synthesized indirectly as, for example, by the action of hydrochloric and hydrobromic acids on appropriate unsaturated 1,4-diketones.[68, 69, 78, 75, 57, 55, 48, 51, 79] The action of the phosphorus pentahalides[52, 46] or bromine[76] on various saturated and un-



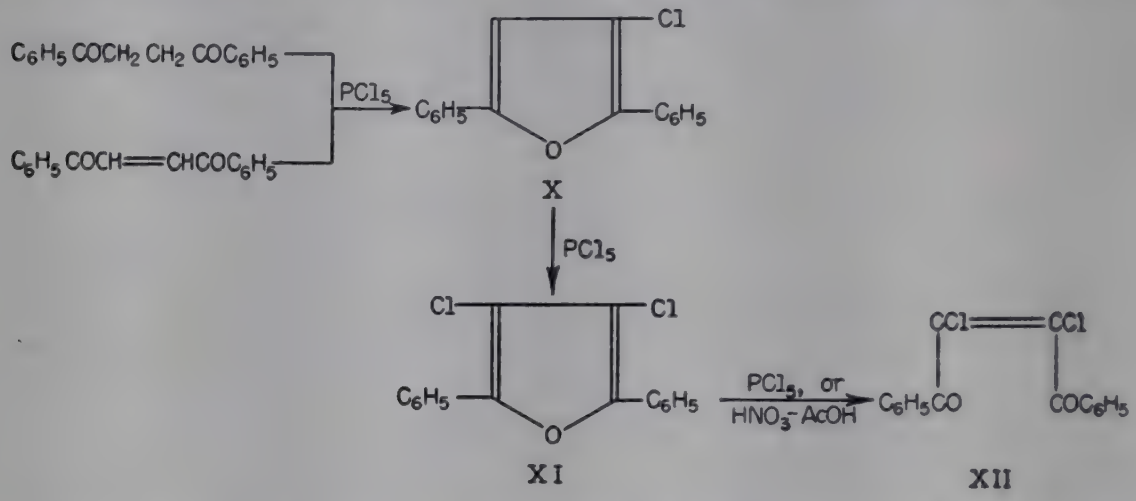
[d] In an earlier paper, this product was erroneously formulated as 2,5-diphenyl-4-acetoxy-3-chlorofuran.[54] Kohler and Woodward[58] showed it to be 2-chloro-2,3-dihydro-2,5-diphenyl-3-furanone (IX).

TABLE 3. ARYLHALOFURANS

Compound	M.p. (°C.)	Ref.
Chlorofurans		
2,5-Diphenyl-3-chloro	76	59, 60, 54; see also 61
2,5-Ditolyl-3-chloro	85	59
2,5-Bis(*p*-bromophenyl)-3-chloro	120	46
2,5-Diphenyl-3,4-dichloro	91	62, 63, 53, 64, 54, 57
2,5-Bis(*p*-bromophenyl)-3,4-dichloro	166	46
2,5-Bis(*p*-acetophenyl)-3,4-dichloro	130.5	65
3,4,5-Triphenyl-2-chloro (?)	168	66
2,4,5-Triphenyl-3-chloro	115, 119	67, 68, 69, 52, 70
2,5-Diphenyl-4-mesityl-3-chloro	102.5–103.5	55
Bromofurans		
2,4-Diphenyl-3-bromo (?)	122	71
2,5-Diphenyl-3-bromo	82–82.5, 84–86	53, 65; see also 72, 73
2,5-Bis(*p*-bromophenyl)-3-bromo	134	45
2,5-Diphenyl-3,4-dibromo	88.5–89	59, 63
2,5-Bis(*p*-bromophenyl)-3,4-dibromo	190–191	44, 45, 74; see also 64, 46
2-(Bromophenyl)-5-(dibromophenyl)-3,4-dibromo	209–210	45
2,5-Dimesityl-3,4-dibromo	146.5–147	47; see also 48
2-(Bromomesityl)-5-mesityl-3,4-dibromo	125.5–126.5	48
2,5-Bis(bromomesityl)-3,4-dibromo	177	48
2-(Bromomesityl)-5-(dibromomesityl)-3,4-dibromo	280–282.5	48
2-(Nitromesityl)-5-mesityl-3,4-dibromo	121.5–122.5	48
2,5-Bis(nitromesityl)-3,4-dibromo	204–205	48
2,4,5-Triphenyl-3-bromo	129	75, 76, 77, 52, 51
2,5-Diphenyl-4-mesityl-3-bromo	126–127	55
2-*p*-Tolyl-4,5-diphenyl-3-bromo	134	75
2-(3,4-Dimethylphenyl)-4,5-diphenyl-3-bromo	137	75
2-(4-Xenyl)-4,5-diphenyl-3-bromo	193	77
2-(*p*-Methoxyphenyl)-4,5-diphenyl-3-bromo	151	75
2-(*p*-Bromophenyl)-4,5-diphenyl-3-bromo	157	75, 77
2-(*p*-Chlorophenyl)-4,5-diphenyl-3-bromo	127	75
2-(3-Methyl-4-chlorophenyl)-4,5-diphenyl-3-bromo	135	75
2,5-Bis(*p*-bromophenyl)-4-phenyl-3-bromo	202.5–203.5	52; see also 69

[55] Lutz and Kibler, *J. Am. Chem. Soc.*, **61**, 3007 (1939).
[56] Lutz and Kibler, *J. Am. Chem. Soc.*, **62**, 360 (1940).
[57] Lutz, Stuart, Wilder and Connor, *J. Am. Chem. Soc.*, **59**, 2314 (1937).
[58] Kohler and Woodward, *J. Am. Chem. Soc.*, **58**, 1933 (1936).
[59] Lutz, *J. Am. Chem. Soc.*, **48**, 2916 (1926).

saturated diketones likewise yields halofurans. Thus, 2,5-diphenyl-3-chlorofuran, X, is formed by treatment of either 1,4-diphenyl-1,4-butanedione or 1,4-diphenyl-2-buten-1,4-dione with phosphorus pentachloride.[54] A second chlorine is introduced by more prolonged action of the reagent giving 2,5-diphenyl-3,4-dichlorofuran, XI, which is itself converted by excess phosphorus pentachloride into the oxidation product, *cis*-1,4-diphenyl-2,3-dichloro-2-buten-1,4-dione, XII. The latter is also formed from XI by the action of nitric acid in glacial acetic acid, a procedure quite generally



applicable to furans from the synthesis of *cis*-unsaturated 1,4-diketones (see [63]).

Almost without exception, the known arylhalofurans possess the halogen atoms in the beta positions of the furan nucleus. It is not surprising, therefore, that in these compounds the halogens are relatively inactive. For example, the bromine atom of 2,4,5-triphenyl-3-bromofuran is unaffected

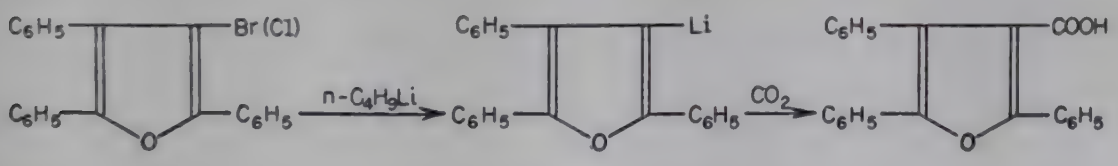
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[60] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 2065 (1934).
[61] Bailey and Hakki, *J. Am. Chem. Soc.*, **71**, 2886 (1949).
[62] Conant and Lutz, *J. Am. Chem. Soc.*, **47**, 881 (1925).
[63] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 978 (1934).
[64] Lutz, Wilder and Parrish, *J. Am. Chem. Soc.*, **56**, 1980 (1934).
[65] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70**, 1359 (1948).
[66] Pütter and Dilthey, *J. prakt. Chem.*, **149**, 183 (1937).
[67] Japp and Burton, *J. Chem. Soc.*, **51**, 430 (1887).
[68] Japp and Klingemann, *Ber.*, **21**, 2932 (1888).
[69] Japp and Klingemann, *J. Chem. Soc.*, **57**, 662 (1890).
[70] Blatt, *J. Am. Chem. Soc.*, **59**, 590 (1936).
[71] Weidlich and Daniels, *Ber.*, **72**, 1590 (1939).
[72] Lutz and Smith, *J. Am. Chem. Soc.*, **63**, 1148 (1941).
[73] Kohler and Engelbrecht, *J. Am. Chem. Soc.*, **41**, 1379 (1919).
[74] Nowlin, *J. Am. Chem. Soc.*, **72**, 5754 (1950).
[75] Allen and Rosener, *J. Am. Chem. Soc.*, **49**, 2110 (1927).
[76] Allen and Herrmann, *J. Am. Chem. Soc.*, **51**, 3591 (1929).
[77] Allen and Wilson, *J. Org. Chem.*, **5**, 146 (1940).
[78] Japp and Maitland, *J. Chem. Soc.*, **85**, 1496 (1904).
[79] Lutz and McGinn, *J. Am. Chem. Soc.*, **65**, 849 (1943).

TABLE 4. MISCELLANEOUS ALKYLARYLHALOFURANS

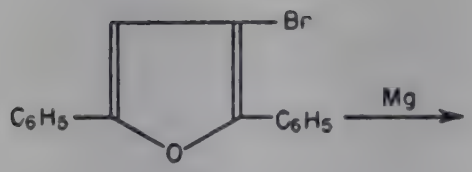
Compound	M.p. (°C.)	Ref.
Chlorofurans		
2,5-Diphenyl-4-methyl-3-chloro	82–82.5	80, 81
2,5-Diphenyl-4-(bromomethyl)-3-chloro	79–86	81
2,5-Diphenyl-4-(N-piperidinomethyl)-3-chloro	76–77	82
2-*t*-Butyl-4,5-diphenyl-3-chloro	87–88	78
Bromofurans		
2,5-Diphenyl-4-methyl-3-bromo	73.5	80, 50, 51; see also 83
2,5-Bis(*p*-bromophenyl)-4-methyl-3-bromo	168–169	50
2,5-Bis(*p*-bromophenyl)-4-(bromomethyl)-3-bromo	212–213	50; see also 83
2,5-Bis(*p*-bromophenyl)-4-(N-diethylaminomethyl)-3-bromo	97–98	83
2,5-Dimesityl-4-methyl-3-bromo	159–160	79
2,5-Dimesityl-4-*t*-butyl-3-bromo	189	49

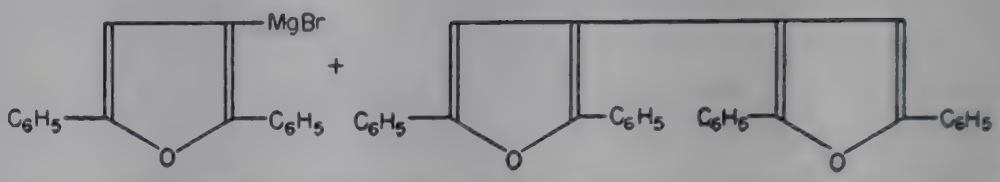
by heating with alcoholic potash for twenty-four hours[75]; or by prolonged boiling with sodium methoxide or ethoxide, although it appears that sodium butoxide will effect replacement.[84] All attempts to react this bromofuran with magnesium[75] or with lithium[85] have been unsuccessful. More recently, however, it has been demonstrated that replacement of the bromine by lithium takes place smoothly by the action of *n*-butyllithium,[86] and that this halogen-metal interconversion may also be applied successfully to the more tightly bound chlorine atom of the related triphenylchlorofuran.



From the less highly phenylated 2,5-diphenyl-3-bromofuran, Lutz and Smith[72] were successful in obtaining a Grignard reagent under special conditions. Some coupling occurred during the reaction, since 2,5,2′,5′-tetraphenyl-3,3′-bifuran was found as a by-product.

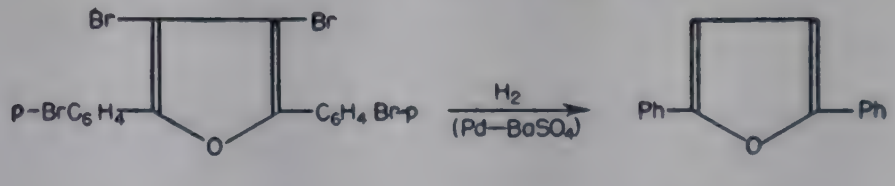
[80] Lutz and Stuart, *J. Am. Chem. Soc.*, **59**, 2316 (1937).
[81] Lutz and Bailey, *J. Am. Chem. Soc.*, **68**, 2002 (1946).
[82] Bailey and Nowlin, *J. Am. Chem. Soc.*, **71**, 732 (1949).
[83] Bailey and Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).
[84] Kohler and Allen, *J. Am. Chem. Soc.*, **46**, 1522 (1924).
[85] Allen and Frame, *J. Am. Chem. Soc.*, **62**, 1301 (1940).
[86] Gilman and Melstrom, *J. Am. Chem. Soc.*, **68**, 103 (1946).

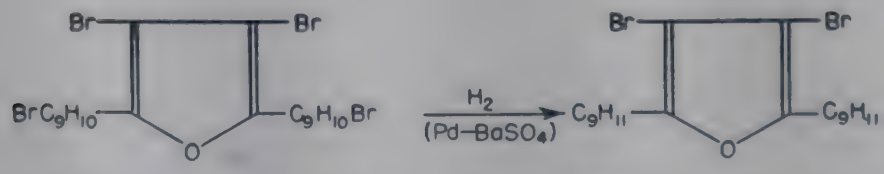




Reductive elimination of halogen by the use of zinc in glacial acetic acid was apparently accomplished successfully in the case of 2,5-bis(*p*-bromophenyl)-3,4-dibromofuran.[45] Either one or both of the bromines attached to the furan nucleus could be replaced by hydrogen, depending upon the experimental conditions, whereas the bromines in the benzene nuclei were uneffected as shown by the isolation of *p*-bromobenzoic acid on subsequent oxidation with chromic acid. On the other hand, the limited utility of this method of reduction is seen by its failure when applied to such related halofurans as 2,4,5-triphenyl-3-bromofuran,[52] 2,5-bisbromomesityl-3,4-dibromofuran,[48] and 2,5-bis(*p*-bromophenyl)-4-methyl-3-bromofuran.[50] Sodium amalgam in boiling alcohol attacked 2,4,5-triphenyl-3-chlorofuran very slowly, eventually giving rise to the expected triphenylfuran.[68, 69]

Catalytic reduction has been employed in several instances. 2,5-Bis(*p*-bromophenyl)-3,4-dibromofuran, for example, is completely dehalogenated with the formation of 2,5-diphenylfuran,[48] whereas the related 2,5-bis-(bromomesityl)-3,4-dibromofuran under similar conditions loses only the bromine atoms attached to the mesityl radicals. Attempts to effect further reduction over platinum oxide or palladium on barium sulfate were unsuccessful; the resistance of the bromines in the furan nucleus is attributed to steric hindrance by the adjacent mesityl groups.[48]

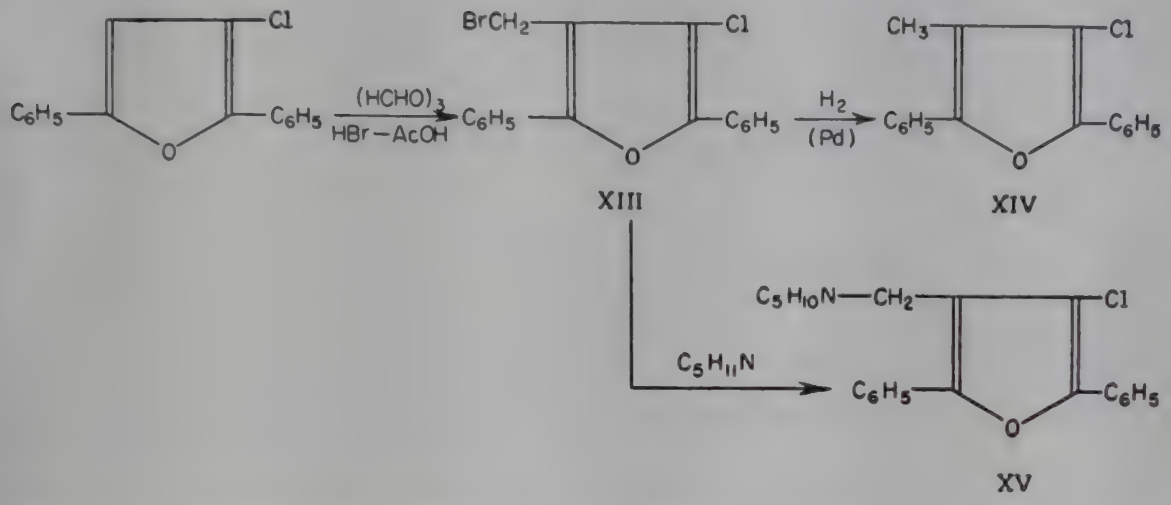




Attempted benzoylation of 2,5-diphenyl-3-bromofuran by the Friedel-Crafts reaction failed.[72] Bromomethylation[e] of the related diphenylchloro-

[e] Attempted chloroethylation using dry hydrogen chloride and paraldehyde resulted in failure.[61]

furan proceeded smoothly to give 2,5-diphenyl-4-(bromomethyl)-3-chlorofuran, XIII, in 79 per cent yield.[81] By catalytic reduction of XIII over a palladium catalyst, the aliphatic bromine atom was removed with formation of 2,5-diphenyl-4-methyl-3-chlorofuran, XIV.[81] With piperidine, XIII is transformed into the corresponding piperidinomethyl derivative, XV[82] (see also [83]).



Halogen Derivatives of Vinylfuran and Ethynylfuran

Bromination of 2-Vinylfuran. In their attempts to synthesize 2-ethynylfuran (furylacetylene), Moureu, Dufraisse, and Johnson[87] studied the bromination of 2-vinylfuran (furylethylene). As a result of this work it appears that, under carefully controlled conditions, it is possible to introduce two atoms of bromine into the side chain leaving the nucleus intact (compare bromination of 3-(2-furyl)acrylic acid, p. 136).

One mole of bromine was added to an ethereal solution of 2-vinylfuran at −10 to −15°. An atmosphere of hydrogen was maintained throughout the reaction in order to avoid complications due to oxidation. Practically no hydrogen bromide was liberated, the reaction proceeding by addition to give a dibromide, I, which because of its great instability, could not be isolated in a pure state. Instead the reaction product, in ether, was treated directly with alcoholic potassium hydroxide in the cold. Under these conditions, one molecule of hydrogen bromide was eliminated to give a monobromo product in which the bromine atom is attached to the side chain as shown by its conversion to 2-ethynylfuran, III, on further dehydrohalogenation using alcoholic potash at 100°. The bromine might be linked to either of the carbon atoms of the lateral chain, however, since loss of hydrogen bromide from I might have occurred in two ways to give either 2-(α-bromovinyl)furan, II, or the isomeric β-bromovinyl compound, or perhaps both. By analogy with the related benzene derivatives, Moureu and his co-workers favored the α-configuration, II, observing that while

[87] Moureu, Dufraisse and Johnson, *Ann. chim.* (*10*), **7**, 13 (1927).

it is very unstable, it can be distilled in a hydrogen atmosphere; b.p. 61–62° (17 mm.), 42–43° (3 mm.). It oxidizes readily in air; and in thin films is converted into a product with strong lachrymatory properties, believed to be 2-furyl bromomethyl ketone,[87] by analogy with the oxidation of α-bromostyrene to bromoacetophenone.[88]

$$C_4H_3O{-}CH{=}CH_2 \xrightarrow[-10°]{Br_2{-}Et_2O} [C_4H_3O{-}CHBr{-}CH_2Br] \xrightarrow[0°]{KOH{-}EtOH}$$

I

$$C_4H_3O{-}CBr{=}CH_2 \xrightarrow[100°]{KOH{-}EtOH} C_4H_3O{-}C{\equiv}CH$$

II III

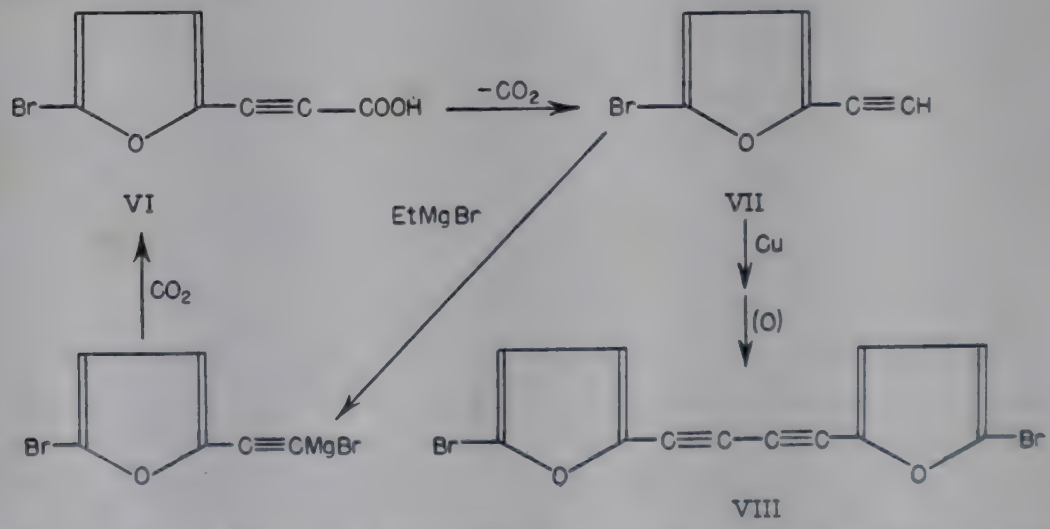
Vinylhalofurans and Ethynylhalofurans.

2-(β-Bromovinyl)-5-bromofuran: V; b.p. 108–112° (14 mm.). Obtained by decarboxylation and dehydrobromination of 2,3-dibromo-3-(5-bromo-2-furyl)propionic acid, IV, when IV is permitted to stand for an extended period in warm water.[89, 90] Oxidation of V, in acetone, with potassium permanganate gives rise to 5-bromo-2-furoic acid in 40 per cent yield.[2]

$$2,5\text{-}C_4H_2O{-}(Br)(CHBr{-}CHBr{-}COOH) \rightarrow 2,5\text{-}C_4H_2O{-}(Br)(CH{=}CHBr)$$

IV V

2-Ethynyl-5-bromofuran: VII; b.p. 63–64° (24 mm.); d_4^{20} 1.509; n_D^{20} 1.5510. Isolated by steam distillation of 5-bromo-2-furylpropiolic acid, VI,[91] and also by the action of alcoholic potash on V.[89, 90]



VIII

1,4-Bis(5-bromo-2-furyl)-1,3-butadiyne: VIII; m.p. 126°. Prepared from VII (via the corresponding copper acetylide) by the action of potassium ferricyanide.[89, 90, 91]

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[88] Dufraisse, *Compt. rend.*, **172**, 162 (1921).
[89] Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).
[90] Gibson and Kahnweiler, *Proc. Am. Acad. Arts Sci.*, **24**, 364 (1888).
[91] Gilman, Hewlett and Wright, *J. Am. Chem. Soc.*, **53**, 4192 (1931).

Halofurancarbinols and Their Derivatives

5-Chlorofurfuryl alcohol: 2,5-C_4H_2O—(Cl)(CH_2OH); m.p. 16–17°; b.p. 46–47° (3 × 10^{-4} mm.). Prepared from 5-chlorofurfural by the Cannizzaro reaction,[92] and also by reduction of 5-chloro-2-furoic ester with lithium aluminum hydride.[93] **Trityl ether,** mp. 100.5–102°. With thionyl chloride in pyridine, the alcohol is converted into the corresponding chloride (too unstable to distill in vacuum), which was transformed into N-substituted-5-chlorofurfurylamines for use in connection with studies of antihistaminic action.[93, 94, 95] **5-Chlorofurfurylamine,** b.p. 50–55° (25 mm.), prepared by reduction (acid-Na-Hg) of 5-chlorofurfural oxime, is much more stable than the corresponding alcohol. The increase in stability is attributed to the ability of the amine to neutralize acidic decomposition products, and thereby to retard auto-decomposition.[93]

5-Bromofurfuryl alcohol: m.p. 43–44°; from the corresponding aldehyde by the Cannizzaro reaction, and also by treating 5-acetoxymethyl-2-furylmercuric bromide with bromine followed by saponification at room temperature.[96] With acetyl chloride in ether, there is formed **5-bromofurfuryl acetate,** b.p. 106–107° (13 mm.); d_{25}^{25} 1.51; n_D^{25} 1.4991.[96] For conversion to N-substituted-5-bromofurfurylamines and the antihistaminic activity of these products, see Vaughan and Anderson,[97] Hayes, Gever and Orcutt,[93] Orcutt *et al.*[94, 95]

(5-Chloro-2-furyl)phenylcarbinol:  formed as an intermediate (not isolated) by the action of phenylmagnesium bromide on 5 -chlorofurfural followed by careful hydrolysis with aqueous ammonium chloride. Under the conditions of the reaction, the carbinol condenses, with loss of water, to form the corresponding *sym.*-ether, **bis-α-(5-chloro-2-furyl) benzyl ether,** m.p. 114.5°.[98] (see also [99]). In the presence of mineral acids, the ether is cleaved and transformed into γ-benzylidenecrotonolactone, a reaction reminiscent of the conversion of unsubstituted furylcarbinols into levulinic acid types (see Chapter 14).

(5-Bromo-2-furyl)phenylcarbinol: isolated in the form of the corresponding *sym.*-ether (m.p. 127–128°) from 5-bromofurfural as in the preceding preparation[98] (see also [99]).

(5-Halo-2-furyl)diphenylcarbinol:  Attempted preparation of the carbinols or the corresponding *sym*-ethers from 5-halo-2-furoic ester and phenylmagnesium bromide was unsuccessful. Even under mild hydrolysis conditions (cold, aqueous ammonium chloride) the intermediate Grignard complex is transformed into

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[92] Hochstein and Wright, *J. Am. Chem. Soc.*, **71,** 2257 (1949).
[93] Hayes, Gever and Orcutt, *J. Am. Chem. Soc.*, **72,** 1205 (1950).
[94] Orcutt and Prytherch, *J. Pharmacol. Exptl. Therap.*, **99,** 479 (1950).
[95] Orcutt, Michaelson, Prytherch and Duprey, *J. Pharmacol. Exptl. Therap.*, **99,** 488 (1950).
[96] Chute, Orchard and Wright, *J. Org. Chem.*, **6,** 157 (1941).
[97] Vaughan and Anderson, *J. Am. Chem. Soc.*, **70,** 2607 (1948).
[98] Gilman, Franz, Hewlett and Wright, *J. Am. Chem. Soc.*, **72,** 3 (1950).
[99] Hewlett, *Iowa State Coll. J. Sci.*, **6,** 439 (1932).

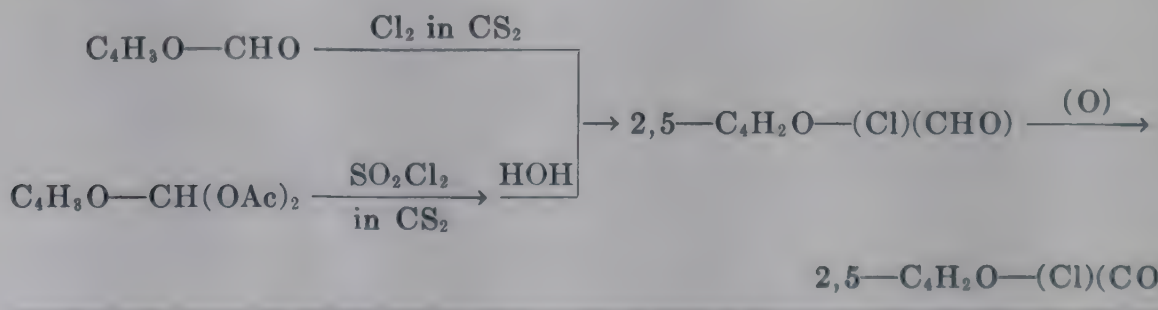
γ-(diphenylmethylene)crotonolactone, indicating that these tertiary alcohols (and their ethers) are even more sensitive toward acidic reagents than are the secondary alcohols (and their ethers) described above.[98]

Halogenated Aldehydes and Ketones

5-Halofurfurals

5-Chlorofurfural (5-chloro-2-furaldehyde) is obtained by the direct action of chlorine on furfural in carbon disulfide as described by Chute and Wright.[100] With no solvent, or when purified carbon disulfide is used, the product yield is in the neighborhood of 1–2 per cent; but the presence of a small amount of sulfur in the carbon disulfide[f] is instrumental in increasing the yield to 12 per cent when one mole of chlorine is employed, and to 24 per cent when the chlorine input is 1.5–2.0 moles per mole of furfural. Iodine inhibits the reaction, as does exposure to sunlight, whereas the addition of benzoyl peroxide increases the yield. Thus, 5-chlorofurfural was obtained in 33 per cent yield by slow addition of chlorine (2 moles) to furfural (1 mole) in boiling carbon disulfide (800 cc.) to which had been added 0.02 g. atom of sulfur and 0.004 mole of benzoyl peroxide. After refluxing for three hours, the solvent was removed and the residue was heated at 100° to complete the evolution of hydrogen chloride. A duplicate experiment without the peroxide resulted in a 24 per cent yield of 5-chlorofurfural, showing that the benzoyl peroxide promotes the activity of the sulfur. The use of a larger quantity of added sulfur markedly impaired the yield of product, whereas additional peroxide (up to 0.016 mole) had no further effect.

Earlier, Gilman and Wright[101] synthesized 5-chlorofurfural in 30 per cent yield (based on the diacetate) by the action of two moles of sulfuryl chloride on furfural diacetate in carbon disulfide. When this preparation was repeated using furfural instead of the diacetate, the product yield was 4–5 per cent. Oxidation with alkaline permanganate converted the chlorofurfural into the known 5-chloro-2-furoic acid, thereby establishing the orientation.

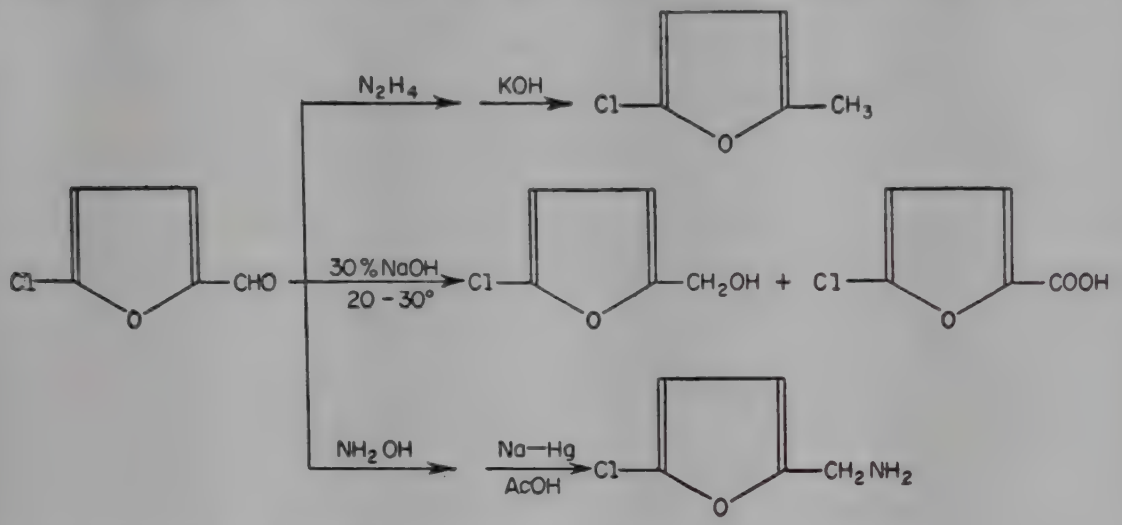


[f] It is interesting that carbon tetrachloride, with or without added sulfur, could not be satisfactorily substituted for carbon disulfide as the chlorination solvent.[100]

[100] Chute and Wright, *J. Org. Chem.*, **10**, 541 (1945).

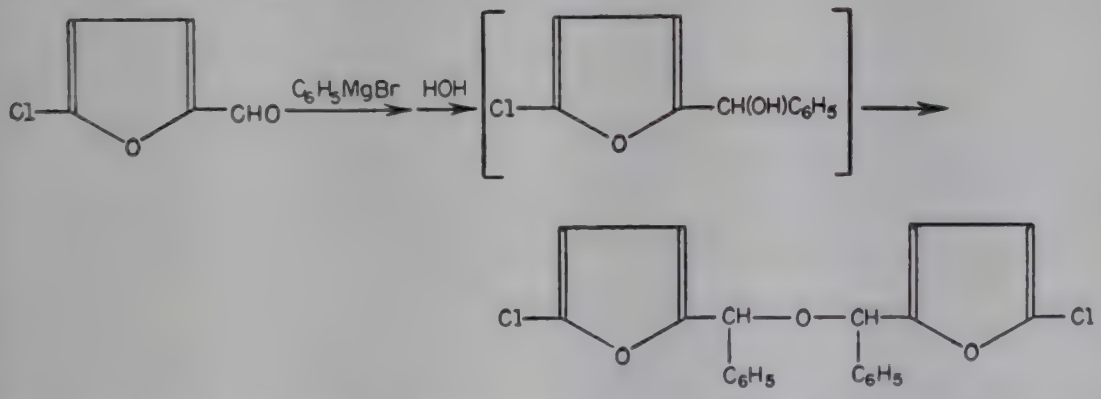
[101] Gilman and Wright, *Rec. trav. chim.*, **50**, 833 (1931).

5-Chlorofurfural is reduced to 5-chloro-2-methylfuran by the Wolff-Kizhner technique.[40] The corresponding alcohol has been prepared by the Cannizzaro reaction; 5-chlorofurfurylamine by reducing the oxime with sodium amalgam in the presence of acetic acid.[92] With methyl acetate and a metal alkoxide, the aldehyde gives rise to methyl 3-(5-chloro-2-furyl)-acrylate[102]; for the condensation with ketene, see Hagemeyer[103]; and with



various amines, see Hayes, Gever and Orcutt.[93]

The Grignard reagent reacts normally with 5-chloro and 5-bromofurfural, but the expected carbinols are not isolable due to facile condensation to the corresponding *sym*-ethers[98] (see also [99]).



Furfural has not been brominated directly, but 5-bromofurfural has been prepared by the action of bromine on furfural diacetate.[105, 106] The preferred procedure involves the addition of two moles of bromine to the diacetate in carbon disulfide at 10°, with an overall reaction time of six hours. Removal of the solvent, and steam distillation of the residue gives

[102] E. I. du Pont de Nemours & Co., Brit. Pat. 569,529 (1945); *C. A.*, **42**, 928 (1948).

[103] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,466,420 (1949); *C. A.*, **43**, 5037 (1949).

[104] Takahashi, Saikachi, Yoshina and Mizuno, *J. Pharm. Soc. Japan*, **69**, 284 (1949); *C. A.*, **44**, 5372 (1950).

[105] Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 1170 (1930).

[106] Schaubler, Jeschke and Beiser, *J. prakt. Chem.*, **136**, 232 (1933).

TABLE 5. HALOGENATED FURFURALS

Substituted furfural	Physical constants (°C.) and derivatives	Ref.
5-Chloro	m.p. 31.5–33, 36 b.p. 70 (10 mm.), 92 (30 mm.) oxime, m.p. 84 semicarb., m.p. 203	101, 100, 104
5-Bromo	m.p. 82, 85 b.p. 112 (16 mm.) diacetate, m.p. 51–52 b.p. 128–130 (5–6 mm.) oxime, m.p. 101, 150–152 semicarb., m.p. 215 (dec.) phenylhydrazone, m.p. 80–85	105, 106, 96
5-Iodo	m.p. 127.5	96

the bromofurfural in 27 per cent yield. Use of either less or more bromine reduces the yield; in the latter instance there is formed, in addition to the bromofurfural, an unidentified product (m.p. 134–135°) which contains two atoms of bromine and gives a positive test with Tollens' reagent.[105]

A pyridine-bromine complex has also been used successfully for brominating furfural diacetate. The reaction was conducted in chloroform, and after three days the mixture was worked up to give 5-bromofurfural in 34 per cent yield.[105]

5-Bromofurfural possesses solubility characteristics similar to those of furfural itself. The bromine atom is firmly attached, and the compound is quite stable. Boiling in aqueous barium carbonate is without effect.[106] Refluxing for ten hours with acetic anhydride gives rise to 5-bromofurfural diacetate in 87 per cent yield.[105]

Alkylation of 5-bromofurfural with *i*-propyl chloride, and aluminum chloride as the condensing agent, introduces an *i*-propyl group at the 4-position. The product was not obtained in a pure state but was oxidized directly to 5-bromo-4-*i*-propyl-2-furoic acid.[107, 108] When *n*-pentyl chloride was used as the alkylating agent, no alkylated product was isolated and most of the bromofurfural was recovered unchanged.[109] In view of the results obtained with ethyl 5-bromo-2-furoate, it had been expected that cleavage of the pentyl chloride would occur with introduction of a butyl radical in the 4-position of the nucleus (p. 122).

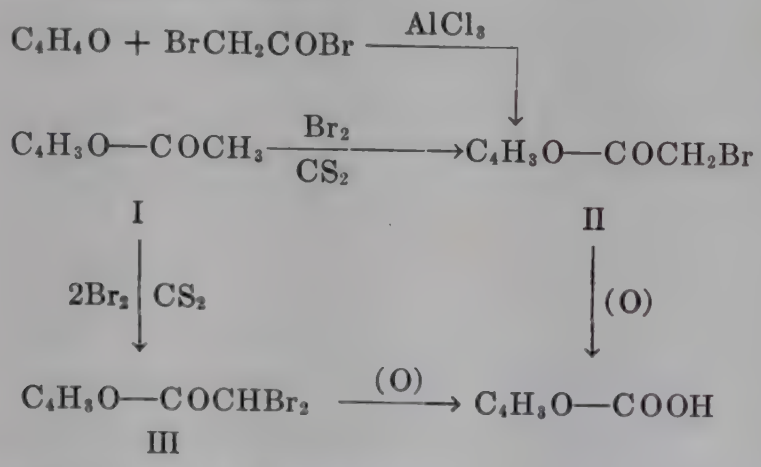
The Cannizzaro reaction with 5-bromofurfural did not succeed using an equivalent quantity of 30 per cent sodium hydroxide, but was effected by employing a large excess of the alkali plus a trace of hydrogen peroxide as a catalyst[96] (see also [106]).

[107] Gilman, McCorkle and Calloway, *J. Am. Chem. Soc.*, **56**, 745 (1934).
[108] Gilman, Calloway and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).
[109] Gilman and Turck, *J. Am. Chem. Soc.*, **61**, 473 (1939).

5-Iodofurfural is also known. It was obtained by the action of iodine on 5-(chloromercuri)furfural in dioxane[96] (see also [106]).

Halogenated Ketones

The direction bromination of 2-furyl methyl ketone, I, results in lateral rather than nuclear substitution, no doubt as a consequence of enolization of the carbonyl group to give a highly active olefinic double bond which adds bromine and then loses hydrogen bromide. Thus, Brown[110] obtained 2-furyl bromomethyl ketone, II, in excellent yield by the introduction of one bromine atom. The structure was established by synthesis of the same product by the Friedel-Crafts reaction of furan with bromoacetyl bromide, and also by the fact that oxidation with alkaline permanganate gives rise to 2-furoic acid. Treatment of I with two moles of bromine gives 2-furyl dibromomethyl ketone, III, the second incoming bromine atom also entering the side chain.[110]



The nuclear brominated 5-bromo-2-furyl methyl ketone and 5-bromo-2-furyl bromomethyl ketone were obtained by indirect means. These, and the other known nuclear halogenated ketones of the furan series are listed below:

5-Bromo-2-furyl methyl ketone: 2,5-C_4H_2O–(Br)($COCH_3$); m.p. 94–95°; oxime, m.p. 79.5°. Obtained in 36 per cent yield by the action of diazomethane on 5-bromofurfural. Also formed in poorer yield by treatment of ethyl 2,3-dibromo-3-(5-bromo-2-furyl)propionate or 2-bromo-3-(5-bromo-2-furyl)acrylyl chloride with strong alkali.[91] Synthesis was also accomplished in 80 per cent yield by acid hydrolysis of ethyl 5-bromo-2-furoyl acetate.[110]

5-Bromo-2-furyl bromomethyl ketone: 2,5-C_4H_2O-(Br)($COCH_2Br$); m.p. 98.5–99.5°. In 50 per cent yield by the action of bromine in carbon disulfide on 5-bromo-2-furyl methyl ketone at room temperature.[110]

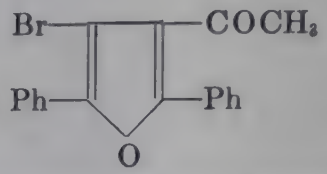
5-Chloro-2-furyl ethyl ketone: 2,5-C_4H_2O-(Cl)(COC_2H_5); m.p. 55°. Formed by the Friedel-Crafts reaction from 2-chlorofuran and propionic anhydride using stannic chloride as the condensing agent. Also obtained by an unusual replacement on reacting 2-nitrofuran with propionyl chloride in the presence of titanium chloride.[111]

[110] Brown, *Iowa State Coll. J. Sci.*, **11**, 221 (1937).
[111] Gilman, Burtner, Calloway and Turck, *J. Am. Chem. Soc.*, **57**, 907 (1935).

5-Bromo-2-furyl phenyl ketone: 2,5-C_4H_2O-(Br)(COC_6H_5); m.p. 37–37.5°; **oxime,** m.p. 139–140°. Prepared by direct bromination of 2-furyl phenyl ketone.[112] For its behavior with phenylmagnesium bromide, see Gilman *et al.*[98]

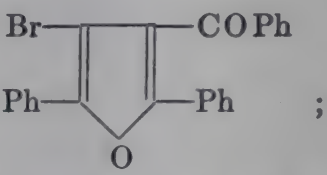
5-Bromo-2-furyl *p*-methoxyphenyl ketone: 2,5-C_4H_2O-(Br)(COC_6H_4OMe-*p*); m.p. 73–74°. Obtained by bromination of 2-furyl *p*-methoxyphenyl ketone. It is stated that an addition product (m.p. 131–132°) is formed initially which loses hydrogen bromide to form the bromofuryl ketone.[112]

4-Bromo-2,5-diphenyl-3-furyl methyl ketone:



; m.p. 81°; from 3-bromo-2,5-diphenylfuran and acetic anhydride under the influence of stannic chloride.[65]

4-Bromo-2,5-diphenyl-3-furyl phenyl ketone:



; m.p. 119.5–120°, 123°. **Oxime,** m.p. 174°. Prepared (a) in 60 per cent yield by the action of bromine on 2,5-diphenyl-3-furyl phenyl ketone in carbon tetrachloride,[72, 113] and (b) by treating 4-carboxy-2,5-diphenyl-3-furyl phenyl ketone (as the silver salt) with bromine.[114]

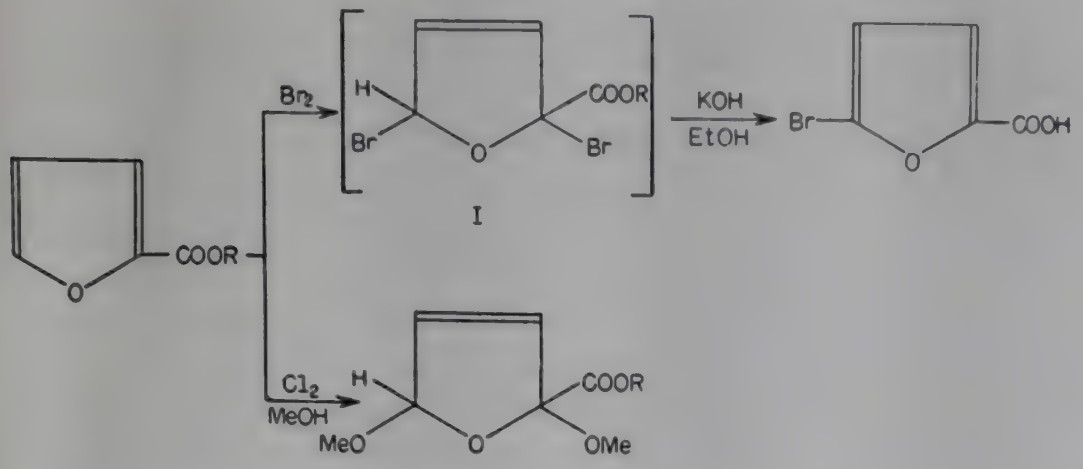
Halogenated Carboxylic Acids

Halo-2-furoic Acids

When exposed to dry bromine or chlorine, 2-furoic acid generally forms a mixture of products rather than one single product. Both substitution and addition products may be isolated, the latter being obtained more readily at low temperatures. As is the case with other furans, the presence of water during the halogenation of furoic acid complicates the reaction, generally bringing about ring cleavage and decarboxylation (p. 496).

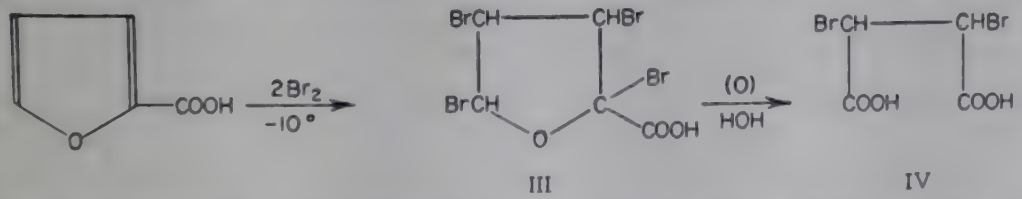
Bromination. The earliest reported work on the action of bromine on 2-furoic acid and its esters is that of Schiff and Tassinari[115] who obtained what they described as a dibromo addition compound of 2-furoic ester. By the action of alcoholic potassium hydroxide on this addition product they isolated what was believed to be a mixture of two isomeric monobromofuroic acids. Later Canzoneri and Oliveri[116] showed only one to exist, namely, 5-bromo-2-furoic acid.[27] In the light of more recent investigations with other furan compounds, Schiff and Tassinari may actually have been dealing with 2,5-dibromo-2-carbethoxy-2,5-dihydrofuran, I (R = C_2H_5). Their work is indefinite, however, and no other investigator

[112] Straley, *Iowa State Coll. J. Sci.*, **11**, 115 (1936).
[113] Kohler and Jones, *J. Am. Chem. Soc.*, **41**, 1249 (1919).
[114] Schmid, Hochweber and Halban, *Helv. Chim. Acta*, **30**, 423 (1947).
[115] Schiff and Tassinari, *Ber.*, **11**, 842 (1878).
[116] Canzoneri and Oliveri, *Gazz. chim. ital.*, **14**, 173 (1884).



has ever reported this dibromo adduct, although the related dimethoxy compound, II (R = CH_3), has been prepared by treating furoic ester with chlorine in methanol.[117, 118]

Ethyl furoate tetrabromide (ethyl 2,3,4,5-tetrabromotetrahydro-2-furoate), m.p. 46–48°, was isolated by Tonnies[119] by treatment of furoic ester with dry bromine at room temperature. That some substitution occurred also was evidenced by the liberation of hydrogen bromide. The tetrabromide of the free acid has been obtained similarly from furoic acid [119]; this preparation was repeated by Hill and Sanger[120, 26] who reported the isolation of 5-bromo-2-furoic acid and its tetrabromide (m.p. 173°) as additional products of the reaction. More recently, Obata[121] has reported 2-furoic acid tetrabromide, III[g] (m.p. 159–160°), in 60 per cent yield by exposing 2-furoic acid to dry bromine at −7 to −10°. III is a colorless, crystalline compound; readily soluble in alcohol and ether, and less so in chloroform. In hot water it decomposes with liberation of carbon dioxide and hydrogen bromide, and on long exposure to cold, dilute chromic acid it is converted into dibromosuccinic acid, IV.



Similar tetrabromo addition compounds have been derived from 5-bromo-

[g] Treatment of III with silver oxide in alcohol gives an unstable, viscous liquid product which decomposes in the air to oxalic acid, and which is converted into glyoxylic acid by the action of lead tetraacetate.[121, 122]

[117] Jones and Imperial Chemical Industries Ltd., Brit. Pat. 595,041 (1947); *C. A.*, **42**, 2992 (1948).

[118] Jones (to Imperial Chemical Industries Ltd.), U. S. Pat. 2,475,097 (1949); *C. A.*, **43**, 7970 (1949).

[119] Tonnies, *Ber.*, **11**, 1085 (1878).

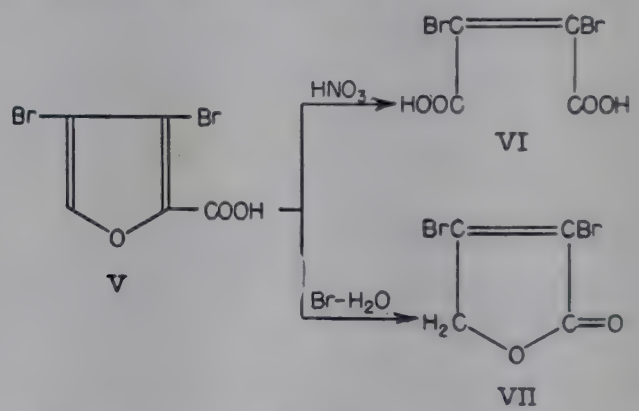
[120] Hill and Sanger, *Ber.*, **17**, 1759 (1884).

[121] Obata, *J. Agr. Chem. Soc. Japan*, **16**, 184 (1940); *C. A.*, **34**, 5841 (1940).

[122] Obata, *J. Agr. Chem. Soc. Japan*, **16**, 187 (1940); *C. A.*, **34**, 5840 (1940).

2-furoic acid[120, 26] and from 2-furamide.[123] The bromine atoms are quite loosely attached and therefore easily removed. For example, Saunders[123] stripped all of the halogen atoms by the action of zinc dust on an alcoholic solution of his 2-furamide tetrabromide (m.p. 121°), and Tonnies[119] reported decomposition, with loss of bromine and hydrogen bromide, by heating ethyl furoate tetrabromide above its melting point. By shaking the latter with mercury in carbon disulfide, ethyl furoate is regenerated.[2]

Tonnies[119] treated furoic acid tetrabromide with alcoholic potassium hydroxide, and obtained a material which analyzed as a dibromofuroic acid (m.p. 184–186°). Later Hill and Sanger[120, 26] found this material to be a mixture of two isomeric dibromofuroic acids melting at 192° and 168°, respectively. The former, obtained in twice the amount of the latter, is 3,4-dibromo-2-furoic acid, V, since oxidation with nitric acid gives dibromomaleic acid, VI.[120, 26] In addition, under selected conditions (see p. 118), the action of aqueous bromine gives α,β-dibromo-γ-crotonolactone, VII.[120, 26, 28] These oxidation products (VI and VII) could only have arisen from a furan in which the bromine atoms are in positions 3 and 4.

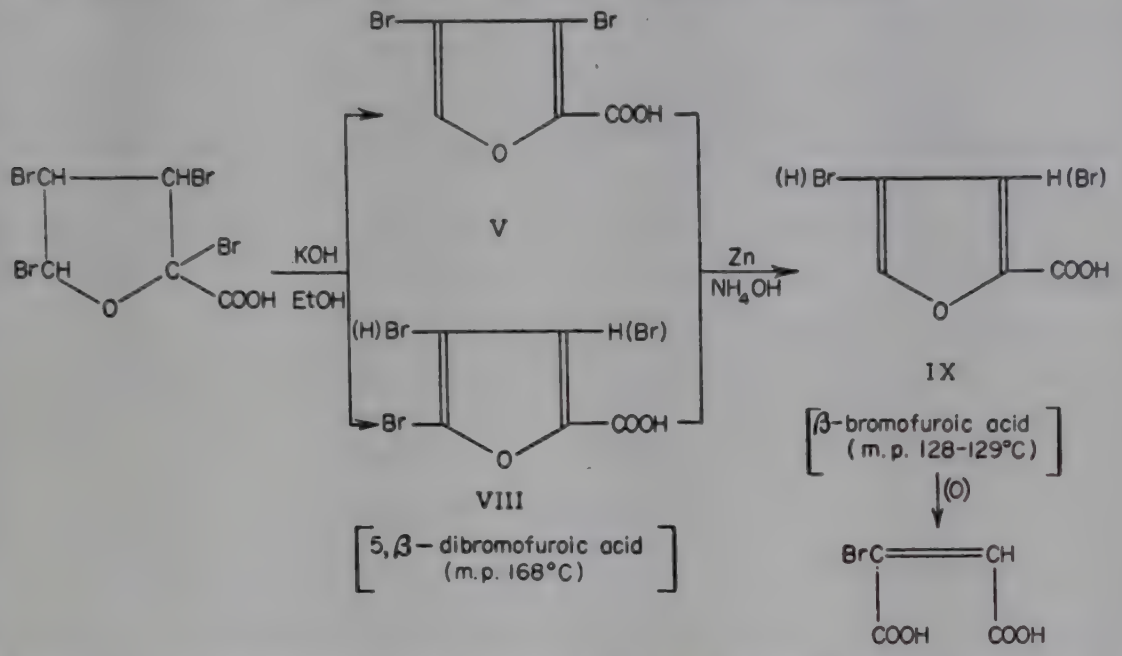


The structure of the isomeric dibromofuroic acid melting at 168°, has been the subject of considerable controversy. It may be obtained directly, in low yield, by treatment of furoic acid at about 100°, with three moles of dry bromine.[h 120, 26, 14] Oxidation gives bromomaleic acid showing that one of the bromine atoms is attached to a beta carbon atom of the furan nucleus.[120, 26] Reduction with zinc dust in ammonia removes one bromine atom with the formation of a bromofuroic acid, IX (m.p. 128–129°). Since the latter is also obtainable by similar reduction of V,[120, 26] its structure must be either 3- or 4-bromo-2-furoic acid (IX), and consequently the dibromo acid in question is either 3,5-dibromo- or 4,5-dibromo-2-furoic acid, VIII. Hill and Sanger considered it unlikely that the 4,5-dibromo acid could arise by dehydrohalogenation of furoic acid tetrabromide, and inasmuch as they had clearly demonstrated the acid melting at 192°, to be

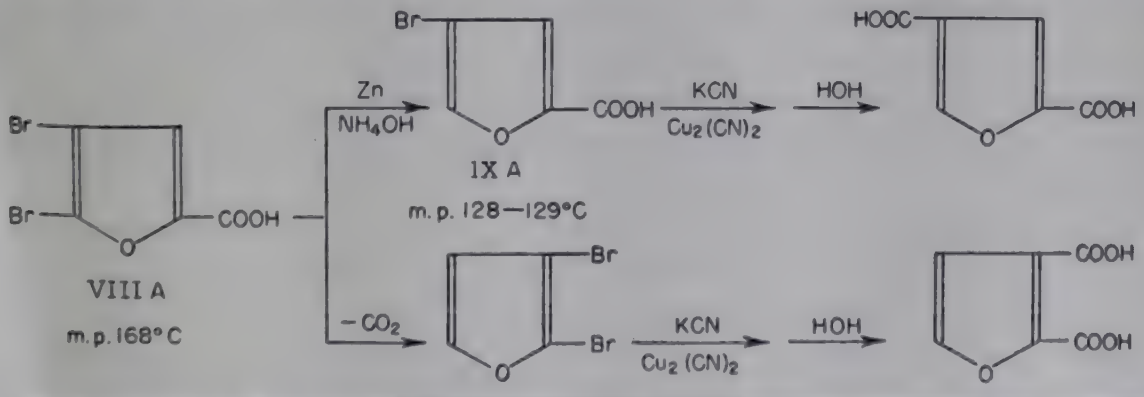
[h] Other products found in the reaction mixture were 5-bromo-2-furoic acid and 2-furoic acid tetrabromide. No 3,4-dibromo-2-furoic acid was isolated.[120, 26]

[123] Saunders, *Am. Chem. J.*, **15**, 130 (1893).

the 3,4-dibromo isomer (V), they proposed that the acid melting at 168° was 3,5-dibromo-2-furoic acid. Accordingly, they concluded that the acid (m.p. 128–129°) obtained by reduction of the latter, was 3-bromo-2-furoic acid. The reactions involved are illustrated in the following diagram, wherein structures VIII and IX are left open to question.



Actually, the experimental results did not warrant designation of the low melting (168°) dibromo acid as 3,5-dibromo-2-furoic acid, since there was no evidence to distinguish between the 3- or 4-carbon atom of the nucleus as the point of attachment of the second bromine atom. Gilman and his students undertook an investigation to clear up this point and proved conclusively that the acid was the 4,5-dibromo isomer, VIII A. It follows that the monobromo acid derived from VIII A by reduction is 4-bromo-2-furoic acid, IX A, and not the 3-bromo isomer as postulated by Hill and Sanger. In both instances, proof of the orientation rests on the synthesis of furandicarboxylic acids of well established constitution[124, 125, 126] (see also [98]). Gilman and his associates[124, 125, 126] obtained VIII A by the



[124] Gilman and Wright, *Chem. Revs.*, **11**, 323 (1932).
[125] Gilman, Vander Wal, Franz and Brown, *J. Am. Chem. Soc.*, **57**, 1146 (1935).
[126] Vander Wal, *Iowa State Coll. J. Sci.*, **11**, 128 (1936).

direct action of bromine (2.65 moles) on furoyl chloride in a manner similar to that employed by Shepard, Winslow and Johnson.[15] The bromine was added at room temperature over a period of two hours, after which the mixture was refluxed for eight hours. Separation of the products was effected by esterification and fractional distillation.[127] Saponification and acidification of the appropriate fraction yielded a product, $C_5H_3Br_2O_3$ (m.p. 154–158°), in 25 per cent yield. Recrystallization of this impure product, which may have been a mixture of 4,5-dibromo- and 3,5-dibromo-2-furoic acids,[15] permitted isolation of the compound sought, namely, the dibromo acid melting at 168–169°. The structure of this acid was proven to be VIII A by its conversion to 2,3-furandicarboxylic acid by the reaction sequences illustrated above. Similarly, the reduction product IX A was converted into the known 2,4-furandicarboxylic acid.

Thus of the three possible dibromo-2-furoic acids only two have been described, the 3,4-dibromo and the 4,5-dibromo isomers. 3,5-Dibromo-2-furoic acid has yet to be isolated.

A similar situation exists with regard to the isomeric monobromo-2-furoic acids. The 4-bromo isomer (IX A) and the 5-bromo acid are known, but 3-bromo-2-furoic acid has not been described to date.

5-Bromo-2-furoic acid, is obtainable directly from 2-furoic acid and bromine. Hill[27, 120, 26] conducted the bromination in glacial acetic acid at 100°; Obata[121, 122] used ether as the solvent at 0°. The yields reported are in the range 35–50 per cent of theory. Whittaker[16] repeated Hill's preparation, and then studied the effect of various solvents and catalysts. His best results (40–45 per cent yield) were obtained at approximately 60° in chloroform or carbon tetrachloride with iodine monochloride or red phosphorus as catalysts, and using 1.75 moles of bromine per mole of furoic acid. The 5-bromo acid has also been prepared in the absence of a solvent. Hill and Sanger[26] report such a procedure, and more recently Raiford and Huey[128] isolated the pure acid in 54 per cent yield by exposing dry furoic acid to slightly more than one mole of bromine vapor at 100°. The melting point reported by the latter investigators is several degrees higher than that reported by any other worker. That the bromine atom occupies the 5-position is established by the fact that decarboxylation gives a bromofuran, the Grignard reagent from which gives rise to 2-furoic acid on carbonation.[15]

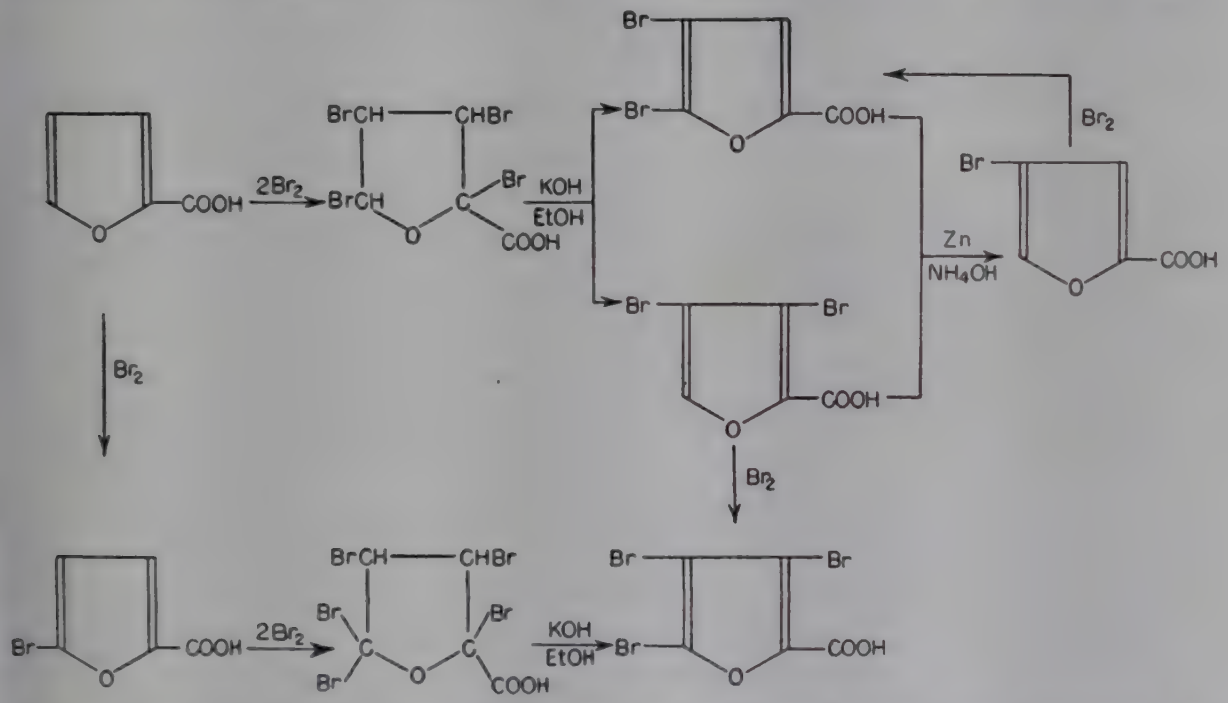
$$2,5\text{—}C_4H_2O\text{—}(Br)(COOH) \xrightarrow{-CO_2} C_4H_3O\text{—}Br \xrightarrow{Mg}$$

$$C_4H_3O\text{—}MgBr \xrightarrow{CO_2} C_4H_3O\text{—}COOH$$

[127] Vander Wal, Thesis, Iowa State College, 1936.
[128] Raiford and Huey, *J. Org. Chem.*, **6**, 858 (1941).

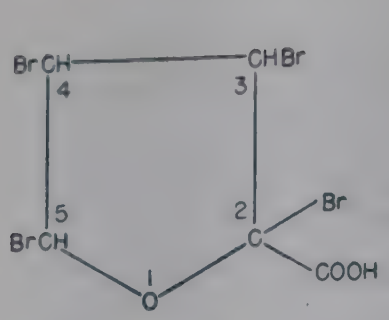
3,4,5-Tribromo-2-furoic acid has not been prepared by direct substitution of furoic acid. According to Hill and Sanger[120, 26] the open β-position of 4,5-dibromo-2-furoic acid (Hill's 3,5-dibromo acid) can not be substituted by bromine. However, the tribromo acid has been obtained by bromination of 3,4-dibromo-2-furoic acid, and also by dehydrohalogenation of 5-bromo-2-furoic acid tetrabromide using strong alcoholic sodium hydroxide at low temperature.[120, 26]

The reactions of 2-furoic acid with dry bromine are summarized, in part, in the following diagram. It is to be emphasized that, in every instance, mixtures of substitution, addition and substitution-addition products are formed, although it is quite probable that, at very low temperature, substitution could be essentially avoided. On substitution, the first incoming bromine atom becomes attached to the open alpha carbon, giving rise to 5-bromo-2-furoic acid. A second incoming atom of bromine is oriented pre-



dominantly to the 4-position, which is in accord with the directing influences recognized in the benzene series. That the 4,5-dibromo-2-furoic acid so obtained is one of the two dibromofuroic acids formed by dehydrohalogenation of furoic acid tetrabromide is of some interest. By 1,2-type elimination of two molcules of hydrogen bromide from the addition compound, one would expect to obtain the 3,4- and 3,5-dibromo acids, yet the 3,5-isomer has not been isolated, whereas the 4,5-dibromo acid is obtained. It is possible to account for the latter by a combination of 1,2 and 1,4-type elimination of two molecules of hydrogen bromide. Klopp and Wright[6] questioned the validity of a mechanism requiring such a 1,4-type elimination, and Gilman and Burtner[130] explained the formation

[129] Hill and Jackson, *Proc. Am. Acad. Arts Sci.*, **24**, 320 (1888).
[130] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

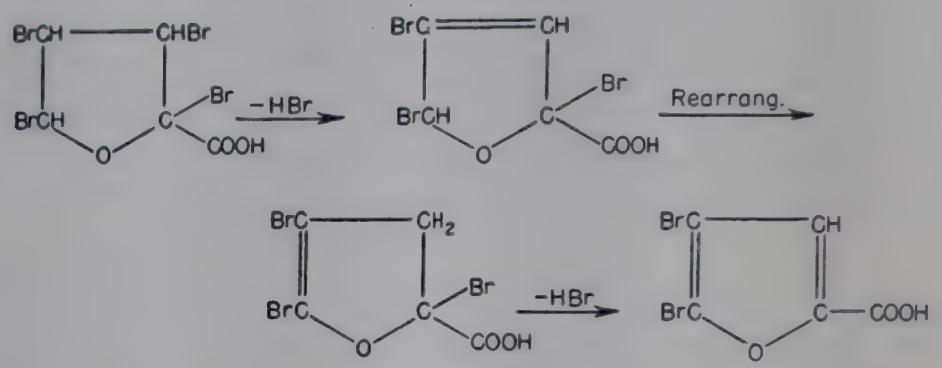


Substituted furoic acid

$-H^3Br^2$; $-H^4Br^5$ → 3,4-dibromo
$-H^3Br^2$; $-H^5Br^4$ → 3,5-dibromo[i]
} 1,2-type elimination

$-H^4Br^3$; $-H^5Br^2$ → 4,5-dibromo—combination 1,2 and 1,4-type elimination

of 4,5-dibromo-2-furoic acid from the tetrabromide as a result of these three steps:



However, 1,4-type elimination from a 2,5-dihydrofuran compound is not unknown. For example, the ready decomposition of Diels-Alder adducts of furan types into their generators can only occur via 1,4-elimination.

Chlorination. As early as 1837, Malaguti[131] observed the rapid absorption of dry chlorine by ethyl furoate. He obtained an oil which gave the correct analysis for a tetrachloro addition compound, and reported carbonization on attempting distillation. In a subsequent paper[132] he called attention to decomposition products formed by the action of alcoholic caustic alkali on the addition compound, but these were not further studied. Many years later, Hill and Jackson[8] succeeded in isolating 3,4-dichloro-2-furoic acid as a product of the alkaline decomposition of ethyl furoate tetrachloride, although they were preceded in publishing the preparation by Denaro.[j133]

The action of chlorine on ethyl furoate, even at 0° results in some substitution as well as addition but it was found, contrary to the report of Malaguti, that the crude reaction mixture could be distilled, under reduced

[i] None of the 3,5-dibromo acid is obtained. It is interesting to observe that Saunders[123] obtained only 3,4-dibromo-2-furoic acid by treatment of 2-furamide tetrabromide with alcoholic caustic alkali. Similarly, only 3,4-dichloro-2-furoic acid was found on alkaline dehydrohalogenation of ethyl 2-furoate tetrachloride.[129]

[j] 3,4-Dichloro-2-furoic acid appears to have been first prepared in 1884 by J. N. Garratt, working with Hill. It was not identified at that time, and the work was completed by Hill and Jackson.[8]

[131] Malaguti, *Ann. chim. phys.* (2), **64**, 275 (1837).
[132] Malaguti, *Ann. chim. phys.* (2), **70**, 372 (1839).
[133] Denaro, *Gazz. chim. ital.*, **16**, 333 (1886).

pressure, without serious decomposition.[129, 134] The various fractions so obtained were treated with alcoholic sodium hydroxide, and examination revealed 5-chloro-2-furoic acid, 3,4-dichloro-2-furoic acid, and a small amount of trichloro-2-furoic acid as the only products. The trichloro acid was obtained as the principal product by carrying out the initial chlorination of ethyl furoate at more elevated temperatures.[8]

The structure of the 3,4-dichloro-2-furoic acid was established by oxidation to a mixture of dichloromaleic acid and α,β-dichloro-β-formylacrylic acid (mucochloric acid). Its identity is further authenticated by its synthesis from 3,4-dichloro-2,5-furandicarboxylic acid by partial decarboxylation.[135]

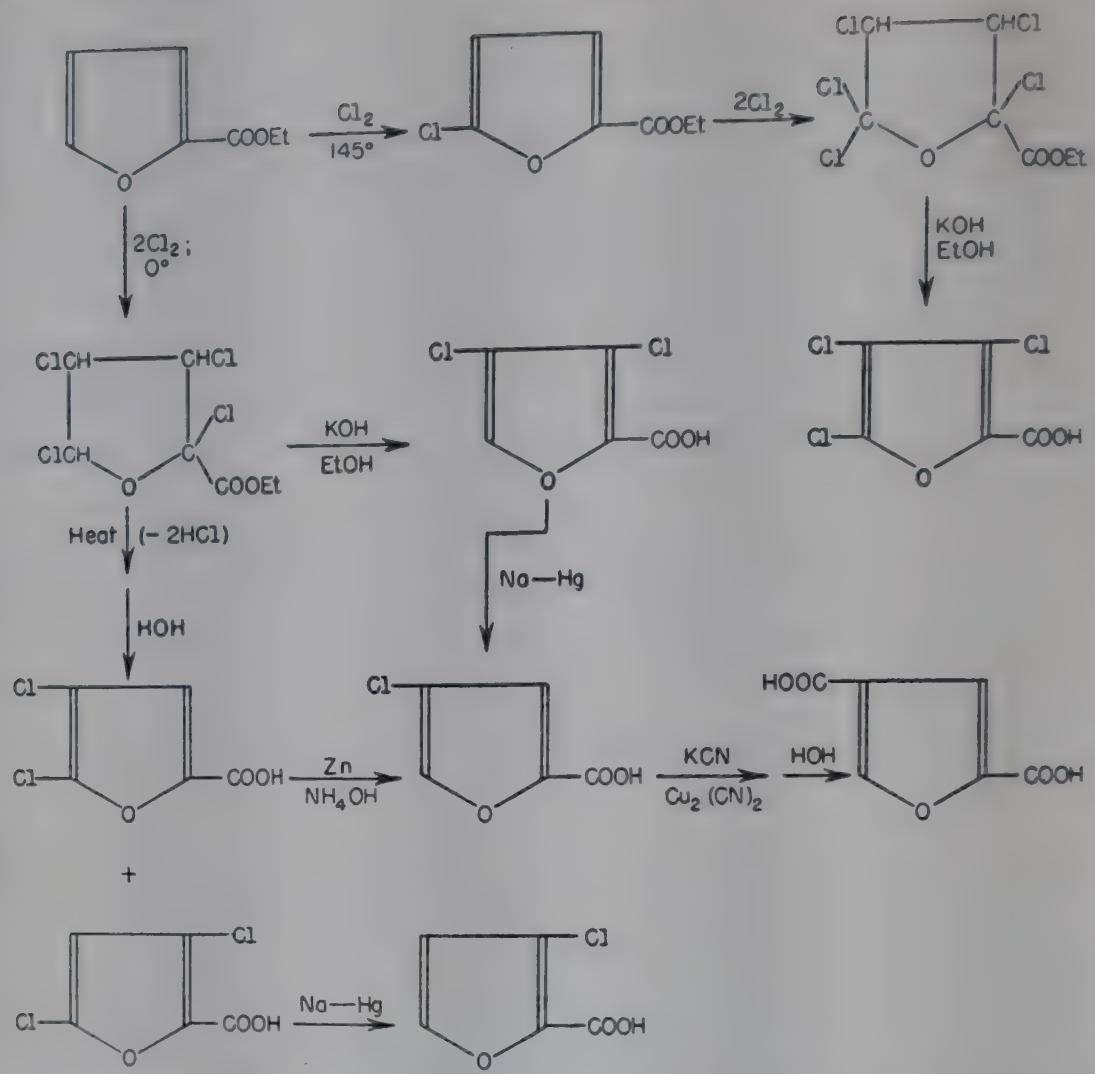
Thus alkaline dehydrohalogenation of ethyl furoate tetrachloride yields only one of the three possible dichloro-2-furoic acids, whereas the tetrabromo addition compound, under similar conditions, gives rise to two of the isomeric dibromo acids. The two remaining dichloro acids were isolated by thermal decomposition of the tetrachloride followed by fractional distillation of the resulting mixed esters, and finally, hydrolysis to the free acids.[8]

To one of these acids, that melting at 155–156°, Hill and Jackson assigned the structure of 3,5-dichloro-2-furoic acid, although adequate proof was lacking. To the other, m.p. 197–198°, no structural configuration was immediately assigned; it being referred to merely as χ-dichloro-2-furoic acid. Later, they[32] suggested that it was either the 4,5-dichloro-acid or a geometrical isomer of the 3,5-dichloro acid. Subsequently, it was erroneously assigned the 4,5-configuration.[28]

Consideration of the oxidation product obtained from these two dichloro acids (chlorofumaric acid in each instance) raises the same question discussed earlier in connection with the characterization of 4,5-dibromo-2-furoic acid. In other words, the oxidation reaction is of no value in differentiating between the 3,5- and 4,5-dichloro structures; it proves that, in each of these isomeric acids, one chlorine atom is in the 5-position, but it does not distinguish between the 3- and 4- nuclear carbon atoms as the point of attachment of the second chlorine.

No clarification was forthcoming until 1936 when Vander Wal[126] (see also [98]) repeated the work of Hill and Jackson, and synthesized the known 2,4-furandicarboxylic acid from the dichlorofuroic acid melting at 156–157°, thereby establishing the structure of the latter as that of 4,5-dichloro-2-furoic acid (not 3,5- as postulated by Hill and Jackson). Inasmuch as the constitution of the 3,4-dichloro acid is well authenticated, the remaining isomer, that melting at 197–198°, must be 3,5-dichloro-2-furoic acid (not 4,5- as assigned by Hill and Cornelison).[28]

[134] Hill and Jackson, *Am. Chem. J.*, **12**, 22 (1890).
[135] Gilman and Vander Wal, *Rec. trav. chim.*, **52**, 267 (1933).



3- and 4-Chloro-2-furoic acids have been prepared only by reduction of the dichloro acids as shown above. One of these was obtained by Hill and Jackson by removal of one chlorine atom from either 3,4-dichloro- or 4,5-dichloro-2-furoic acid. Vander Wal's work shows this to be the 4-chloro acid. The 3-chloro isomer was obtained by reduction of 3,5-dichloro-2-furoic acid with sodium amalgam.

5-Chloro-2-furoic acid may be prepared by direct substitution. It is also obtained as a by-product in the preparation of ethyl furoate tetrachloride. Treatment of ethyl furoate with chlorine at 145°, until the gain in weight corresponds to the substitution of one chlorine atom gives 5-chloro-2-furoic ester in 38 per cent yield.[32] By chlorination of furoyl chloride at 100°, Hewlett[136] reports a 66 per cent yield of 5-chloro-2-furoyl chloride.

3,4,5-Trichloro-2-furoic acid was prepared by the action of alcoholic potassium hydroxide on ethyl 5-chloro-2-furoate tetrachloride.[32]

Physical Properties. As has been shown, the structures assigned by Hill and his co-workers to several of the halogenated 2-furoic acids were incorrect. In the table which follows, and throughout the remainder of the book, Hill's designations have been revised in accordance with the pre-

[136] Hewlett, Thesis, Iowa State College, 1931.

TABLE 6. HALO-2-FUROIC ACIDS

Substituted 2-furoic acid	M.p. (°C.)	Derivatives (°C.)	Ref.
5-Chloro	176–177, 179–180	esters: methyl, m.p. 40–42 ethyl, b.p. 88 (5 mm.), 216–218 (768 mm.) acid chloride, b.p. 92–95 (10 mm.) amide, m.p. 154–155	129, 134, 15, 23, 137, 136, 127, 42
4-Chloro	145–146, 148.5–149.5	ethyl ester, m.p. 29–30 b.p. 217 (764 mm.)	129, 134, 15, 23, 127
3-Chloro	153.5–154.5	—	127
3,4-Dichloro	167–168, 169.5–170.5	ethyl ester, m.p. 63–64 amide, m.p. 176	133, 8, 129, 134, 15, 135
3,5-Dichloro	197–198	ethyl ester, m.p. 72–73 b.p. 122.5 (16 mm.)	129, 32
4,5-Dichloro	155–156, 156–157	ethyl ester, m.p. 2–3 b.p. 116–118 (16 mm.) amide, m.p. 153–154	129, 134, 137
3,4,5-Trichloro	172–173, 174.5–175.5	ethyl ester, m.p. 62–63 amide, m.p. 160–161	129, 32
5-Bromo	185, 190–191	esters: methyl, m.p. 59–72 ethyl, m.p. 17 b.p. 133–134 (31 mm.), 235 (767 mm.) acid chloride, m.p. 54–56 b.p. 89 (8 mm.) amide, m.p. 144–145, 146 anilide, m.p. 145	27, 26, 137, 16, 127, 121, 128, 25, 138, 42
4-Bromo	128–129	ethyl ester, m.p. 28–29 b.p. 235–236 (768 mm.) amide, m.p. 155–156	26, 14, 15
3,4-Dibromo	184–186, 191	ethyl ester, m.p. 67–68 amide, m.p. 195–196	119, 26
4,5-Dibromo	167–168, 170.5–171.2	ethyl ester, m.p. 57–58 b.p. 271–272 (765 mm.) acid bromide, m.p. 45.6 amide, m.p. 175–176	26, 14, 137, 24
3,4,5-Tribromo	218–219	ethyl ester, m.p. 104 amide, m.p. 222–223	26
5-Iodo	192, 193	—	139, 137
3,4-Dichloro-5-bromo	185–186	—	8, 129, 32
3,4-Dibromo-5-chloro	193–194	—	129, 32

ceding text. In summary:

Hill's:	Is actually:
3-Bromo-2-furoic acid	4-Bromo-2-furoic acid
3,5-Dibromo-2-furoic acid	4,5-Dibromo-2-furoic acid
3-Chloro-2-furoic acid	4-Chloro-2-furoic acid
3,5-Dichloro-2-furoic acid	4,5-Dichloro-2-furoic acid
x, or 4,5-dichloro-2-furoic acid	3,5-Dichloro-2-furoic acid

The location of the halogen substituents in the known sulfo-halofuroic acids (p. 126) and nitrohalofuroic acids (Chapter 4) has also been corrected, where necessary, to conform to the orientation indicated.

Chemical Properties. *Action of Dry Bromine.* The action of dry bromine on halogenated furoic acids has been mentioned earlier, but a few additional remarks are warranted.

Furoic acids substituted by halogen in positions 3- or 4- appear not to form addition products on exposure to dry bromine at ordinary temperatures. Whereas 5-bromo-2-furoic acid is converted into a stable tetrabromide under these conditions, no similar products are reported from the 3,4-dibromo-, 3,4-dichloro-, or 4-bromo-2-furoic acids.[26, 120, 134, 32, 8, 129] In the last three instances, slow substitution occurs at the open 5-position with introduction of a bromine atom. Thus 4-bromo-2-furoic acid yields the 4,5-dibromo acid after two days exposure to bromine vapor at room temperature.

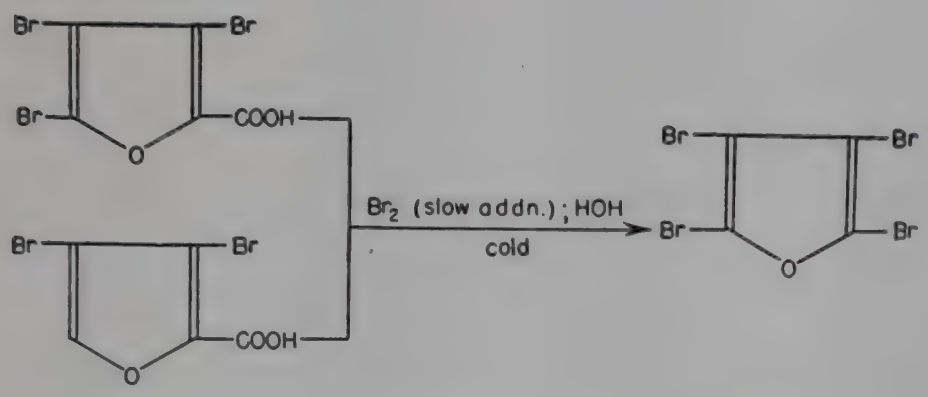
As mentioned previously, the 3-position in 4,5-dibromo-2-furoic acid resists substitution by bromine[26, 120] and while one would anticipate similar behavior on the part of the corresponding dichloro acid, the problem awaits investigation. Likewise, no attempt has been made to halogenate 3,5-dichloro-2-furoic acid, which might be expected to substitute in the 4-position by analogy with its reported sulfonation (see p. 128).

Action of Aqueous Bromine. It was mentioned earlier that oxidative degradation of halo-2-furoic acids to maleic and fumaric acids, or to halogenated derivatives of these acids, is a useful means of distinguishing between alpha and beta halogen atoms. With aqueous bromine as the oxidizing agent, the over-all reaction may involve several steps including replacement-decarboxylation, addition, hydrolysis and in some cases, further substitution. This is apparent from a consideration of the products which have been isolated under variously controlled conditions.

On relatively slow addition of one mole of bromine to a cold, alkaline solution of 5-bromo-2-furoic acid, carbon dioxide is evolved with the formation of 2,5-dibromofuran.[3] Similarly tetrabromofuran is formed from 3,4,5-tribromo-2-furoic acid,[26] and 2-bromo-3,4,5-trichlorofuran from the corresponding trichlorofuroic acid.[129, 32] Thus, it is evident that the carboxyl group of halo-2-furoic acids is easily replaced by the action of aqueous bromine.

Under similarly mild conditions, bromine substitution may occur at an

open alpha position.[k] In this way, Hill and Sanger[26] obtained a considerable quantity of tetrabromofuran (along with unchanged acid) by slow addition of one mole of bromine to cold, aqueous 3,4-dibromo-2-furoic acid. As will be shown later, rapid addition of the bromine produces α,β-dibromo-γ-crotonolactone.



When sufficient bromine is employed, addition may occur, as in the formation of 2,5-dibromofuran tetrabromide, I,[1] by rapid addition of three moles of aqueous bromine to 5-bromo-2-furoic acid.[27, 3] In this instance, if the aqueous reaction mixture is permitted to stand for a lengthy period, 2,3-dibromosuccinic acid, II, is found as a product along with some fumaric acid.[27] The dibromosuccinic acid may have its origin in the hydrolysis of I,[3] and/or the addition of bromine to the maleic and fumaric acids also formed in the reaction.[140, 141] Maleic acid is most likely obtained by hydrolysis of 2,2,5,5-tetrabromo-2,5-dihydrofuran, III, although the latter has not been isolated. Isomerization of the maleic acid would account for the formation of fumaric acid, which may be obtained in 60 per cent yield by slow diffusion of two moles of bromine vapor into a cold, aqueous solution of the 5-bromo acid. More rapid addition of three moles of bromine, followed by long standing, gives less fumaric acid and an increased amount of dibromosuccinic acid.[27, 26] Accordingly, it would appear that the nature

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[k] In some instances this substitution of an alpha hydrogen atom may precede replacement-decarboxylation. Thus, Hill and Jackson[8] obtained 5-bromo-3,4-dichloro-2-furoic acid by the action of cold, aqueous bromine (one mole) on 3,4-dichloro-2-furoic acid.

[1] Two isomeric forms of 2,5-dibromofuran tetrabromide were reported; so-called alpha and beta forms, melting at 110–111°, and 55°, respectively, the latter in insignificant amounts. Both gave dibromosuccinic acid on hydrolysis[3].

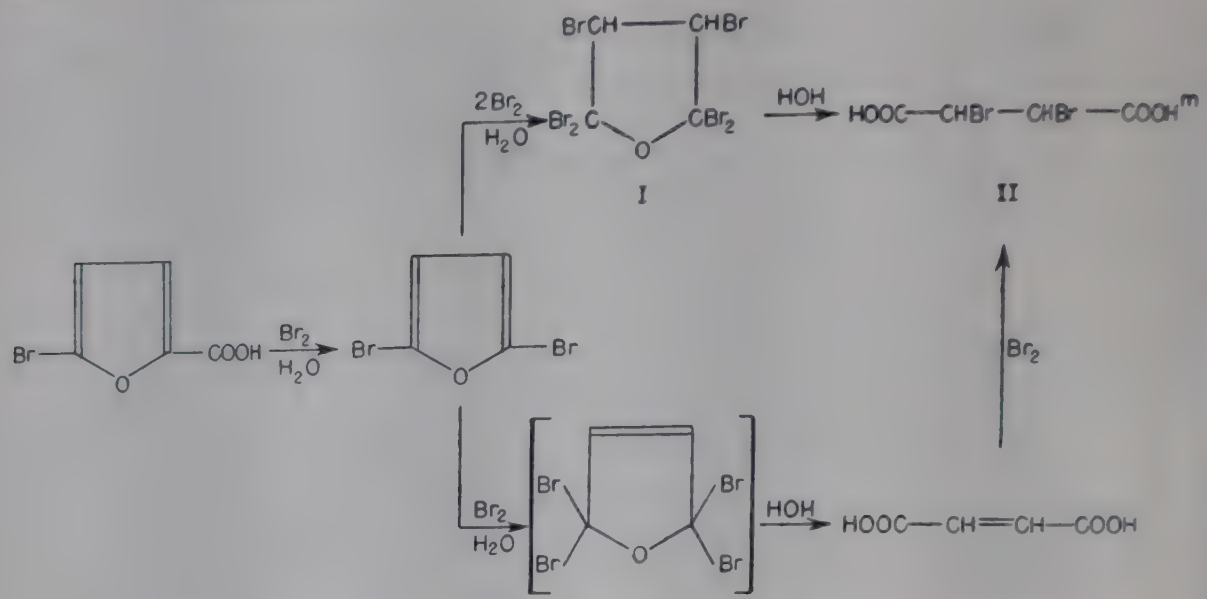
[137] Gilman, Janney and Bradley, *Iowa State Coll. J. Sci.*, **7**, 429 (1933).

[138] Benkeser and Currie, *J. Am. Chem. Soc.*, **70**, 1780 (1948).

[139] Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931).

[140] Kekulé, *Ann. suppl.*, **1**, 338 (1861).

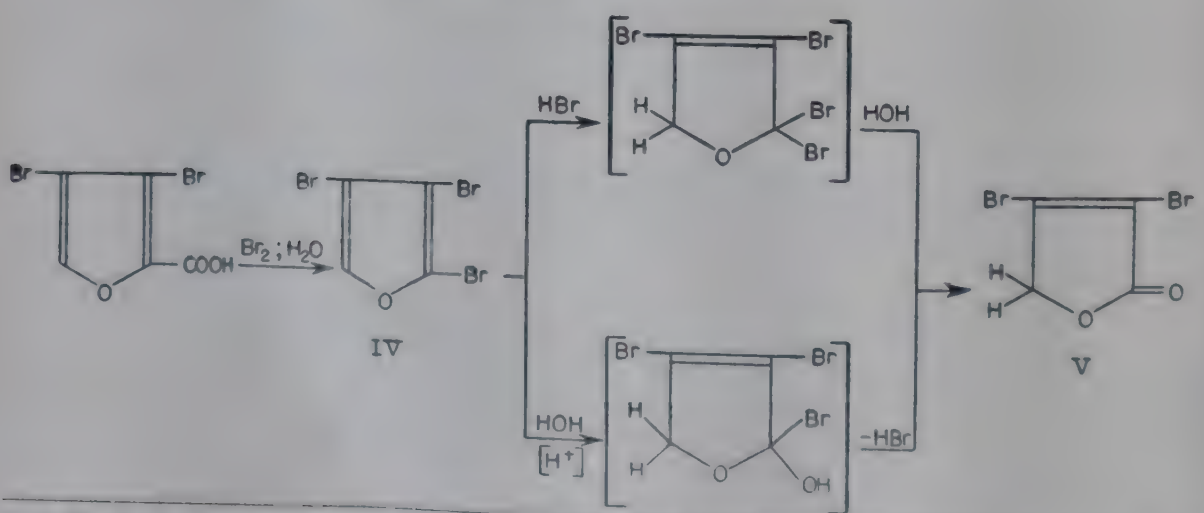
[141] Fittig, *Ann.*, **195**, 56 (1879).



I II III

of the products obtained varies with the quantity of bromine employed, the rate of bromine addition, and the extent of the hydrolysis step.

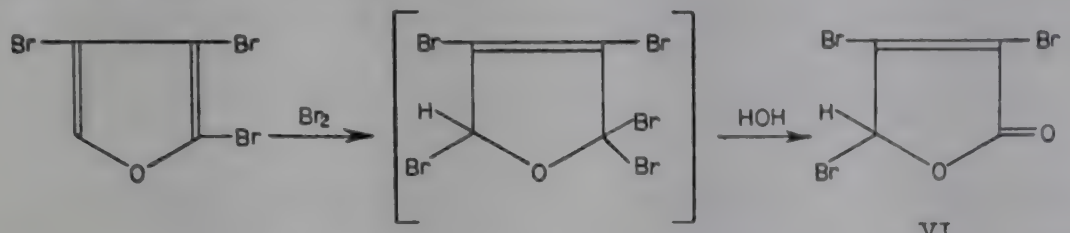
Further studies of the action of bromine on aqueous bromo- and chloro-2-furoic acids are reported by Hill and Cornelison.[28] Under closely controlled conditions they were able to isolate compounds of an intermediate degree of oxidation, namely, crotonolactone and its halogenated derivatives. Rapid addition of one mole of aqueous bromine to 3,4-dibromo-2-furoic acid in the cold yielded a crystalline compound, $C_4H_2Br_2O_2$, identified as α,β-dibromo-γ-crotonolactone, V.[28] This product had previously been obtained by Hill and Sanger,[26] and is apparently identical to that described by Tonnies[142] who had considered it to be dibromofumaric aldehyde. Hill and Cornelison proposed the following mechanism based on the ready replacement of the alpha carboxyl group, and on facile 1,4-addition of hydrobromic acid (or of HOH under the influence of hydrogen ion) to the postulated intermediate tribromofuran, IV:



IV V

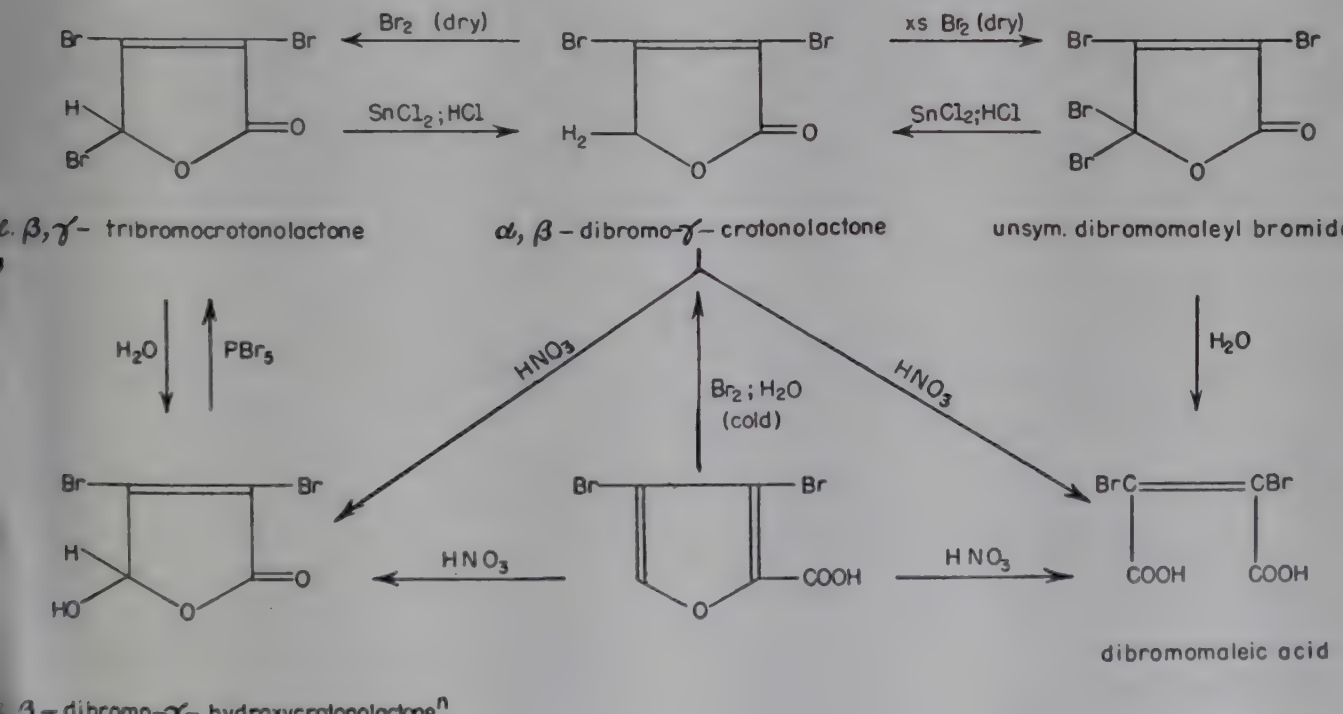
[m] Both the low melting dibromosuccinic acid (m.p. 165°) and its higher melting isomer (dec. 203°) were obtained.[27, 3]

α,β,γ-Tribromo-γ-crotonolactone (mucobromyl bromide), VI, was also formed as a product of the reaction. This is accountable by similar reasoning wherein bromine adds to the initial tribromofuran as indicated below. It is interesting to observe that these applications of the theory of 1,4-addition to a 1,3-dienic system precede by several years Thiele's classic exposition of this hypothesis.



VI

The relationship of these products to each other and to those of a more advanced degree of oxidation of 3,4-dibromo-2-furoic acid is shown in the following diagram which illustrates some of the transformations carried out by Hill and his co-workers. The validity of the lactone structures proposed for several of these compounds is indicated by their interconversion, and by their reduction to produce the dibromocrotonolactone in high yield.



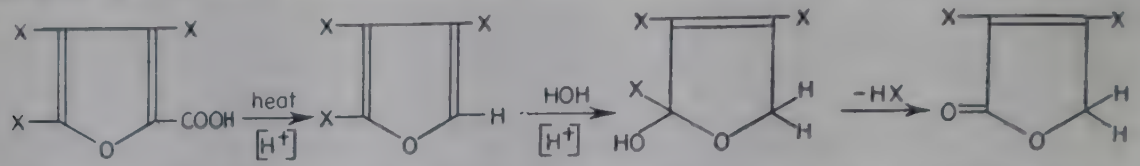
In a similar manner 3,4-dichloro-2-furoic acid is converted to α,β-dichloro-γ-crotonolactone,[28] whereas with an excess of aqueous bromine in the cold, or by the action of hot, dilute nitric acid, oxidation proceeds

[n] Hemiacylal form of α,β-dibromo-β-formylacrylic acid.

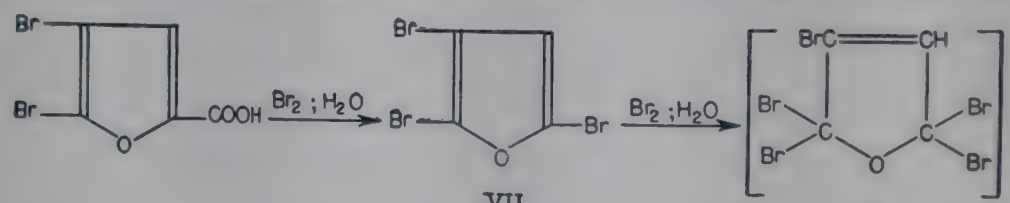
[142] Tonnies, *Ber.*, **12**, 1202 (1879).

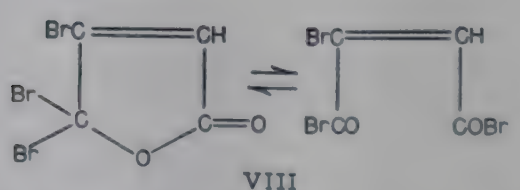
further with the formation of α,β-dichloro-γ-hydroxy-γ-crotonolactone (mucochloric acid) and dichloromaleic acid.[8, 129, 134]

Dihalocrotonolactone types are also obtainable from tribromo- and trichloro-2-furoic acids by boiling with mineral acids, preferably concentrated hydrobromic acid, less readily with hydrochloric or sulfuric acids. Hill and Cornelison formulated the transformation in the following manner:



Other 5-halo-2-furoic acids undergo similar oxidative degradation when heated with aqueous mineral acids. Thus a monobromocrotonolactone (m.p. 58°) is formed by the action of hydrobromic acid on 4,5-dibromo-2-furoic acid. As a consequence of their error in designating the latter as the 3,5-dibromo acid, Hill and Cornelison refer to the product as the β-bromo lactone whereas it is altogether probable that it is the α-bromo isomer. What may possibly be the true β-bromo-γ-crotonolactone (m.p. 77°) was obtained by reduction of so-called bromomaleyl bromide, VIII, resulting from the action of two moles of aqueous bromine on 4,5-dibromofuroic acid. To this isomer, Hill and Cornelison assigned the α-bromo configuration. In this particular reaction supporting evidence was obtained for the belief that replacement-decarboxylation is the first step of reaction with aqueous bromine. The intermediate tribromofuran, VII, was isolated, which with aqueous bromine gave the same "bromomaleyl bromide" (m.p. 54–55°) as was obtained from the dibromofuroic acid.

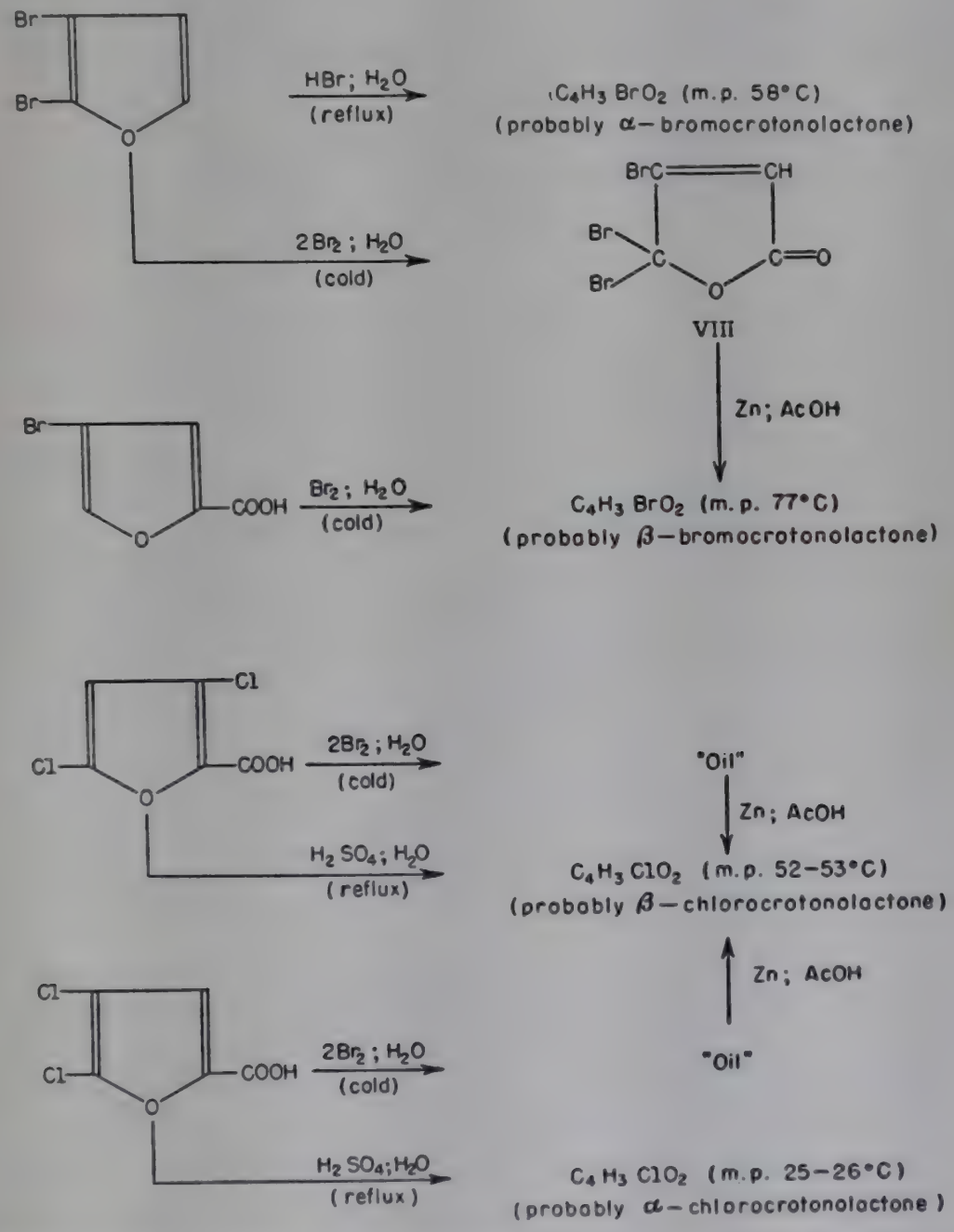




A similar question arises in connection with the structures assigned to the isomeric chlorocrotonolactones. As expected, when 3,5-dichloro- and 4,5-dichloro-2-furoic acids are heated with mineral acid two different lactones are obtained. However, only one of these is obtained by the action

of two moles of aqueous bromine on either acid followed by reduction of the intermediate "oily" product.[28]

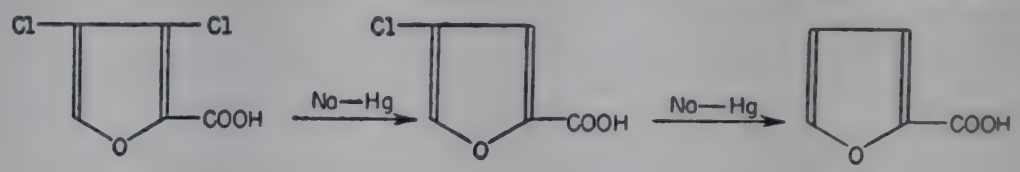
These reactions are summarized in the diagram which follows. The structures of each of the initial halo-2-furoic acids have been corrected, and the probable orientation of the substituted lactone products is indicated. In essence, the latter is exactly the reverse of that suggested by Hill and Cornelison; that is, alpha where Hill and Cornelison propose beta, and vice versa. It remains for some future investigator to clarify the problem.



Reduction. With halofuroic acids, as with other organic halides, bromine is more easily replaced by hydrogen than is chlorine. In addition, alpha halogen substitutents are more reactive than those occupying a beta nuclear

position. Thus 4,5-dibromo-2-furoic acid in cold, ammoniacal solution is reduced slowly to 4-bromo-2-furoic acid by the action of zinc dust.[26] With the same reducing agent, heat is required in order to replace the alpha chlorine atom of the corresponding dichlorofuroic acid.[129]

Zinc and ammonia have little action on 3,4-dichloro-2-furoic acid,[124, 143] although the 3,4-dibromo acid is reduced by this reagent to 4-bromo-2-furoic acid.[26] By boiling an alcoholic solution of the dichloro acid, I, with sodium amalgam, the chlorine atom in the 3-position is removed with the formation of 4-chloro-2-furoic acid, II.[134] When an excess of sodium amalgam is employed, reduction proceeds all the way to furoic acid[143] as is also the case on similar treatment of 3,5-dichloro-2-furoic acid.[134]

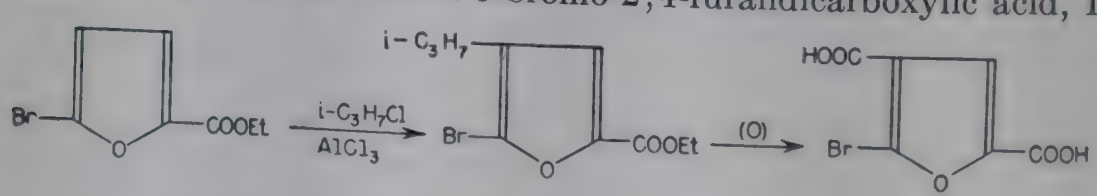


I II

It is apparent that there is a differential reactivity on the part of halogen atoms in the 3- and 4-positions; that the halogen adjacent to the carboxyl group is the more readily replaced by hydrogen.

5-Chloro-2-furoic ester is reduced by lithium aluminum hydride to 5-chlorofurfuryl alcohol in practically quantitative yield.[93]

Alkylation by the Friedel-Crafts Reaction. Condensation of a 5-halo-2-furoic ester with an alkyl halide in the presence of aluminum chloride introduces an alkyl group at the 4-position.° For example, reaction of ethyl 5-bromo-2-furoate with isopropyl chloride gives ethyl 5-bromo-4-*i*-propyl-2-furoate, I, in 35 per cent yield. The location of the alkyl group is known by oxidation of I to the known 5-bromo-2,4-furandicarboxylic acid, II.[108]



I II

With tertiary butyl chloride as the alkylating agent, only three per cent of ethyl 5-bromo-4-*t*-butyl-2-furoate could be isolated,[144] although the same product is reported in much higher yield using *n*-butyl chloride.[109] Quite unexpectedly, *n*-pentyl chloride and *n*-hexyl bromide likewise gave ethyl 5-bromo-4-*t*-butyl-2-furoate as the product, as did *n*-octadecyl bromide in 46 per cent yield along with isobutane (32 per cent) and butane

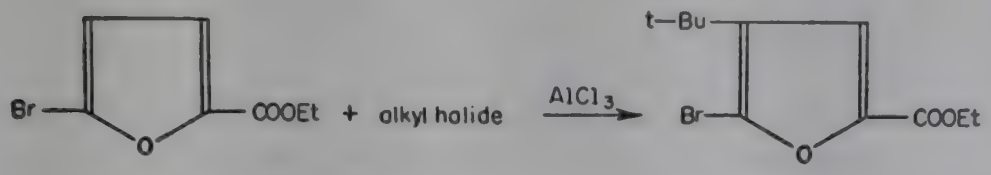
° The properties of the alkylhalo-2-furoic acids are listed in Table 8.

[143] Hill and Hendrickson, *Am. Chem. J.*, **15**, 145 (1893).

[144] Gilman and Burtner, *J. Am. Chem. Soc.*, **57**, 909 (1935).

(7 per cent).[144, 109] Gilman and Turck[109] concluded that the higher *n*-alkyl halides (C_4-C_{18})invariably introduce a *t*-butyl radical into 5-bromo-2-furoic ester.

TABLE 7. ALKYLATION OF 5-BROMO-2-FUROIC ESTER[109]



Alkyl halide	4-*t*-Butyl ester (% yield)
n-C_4H_9Cl	26
t-C_4H_9Br	15
n-$C_5H_{11}Cl$	15
t-$C_5H_{11}Cl$	6
i-$C_5H_{11}Br$	20
n-$C_5H_{11}I$	25
n-$C_6H_{13}Cl$	20
n-$C_6H_{13}Br$	6
n-$C_{12}H_{25}Br$	13
n-$C_{16}H_{33}Br$	20
n-$C_{18}H_{37}Br$	46

This is a most interesting observation, implying as it does, not only degradation of alkyl groups C_5 or higher to a C_4 group, but also rearrangement in every case so that the entering butyl radical has the tertiary configuration. The tendency for rearrangement of alkyl groups in the Friedel-Crafts reaction is well-known, but for the most part, this isomerization involves only migration of hydrogen atoms and not rearrangement of the carbon skeleton. Thus, there is no evidence for migration of a methyl group of the alkyl radical during alkylation of benzene with aluminum chloride as the catalyst, except in the case of alkylation with neopentyl chloride.[145] It would appear, therefore, that alkyl halides undergo much more extensive rearrangement with furans (see also Chapter 12) than with aromatic types.

It is unfortunate that the published information is somewhat inconclusive in establishing this seemingly exceptional behavior. The sole experiment cited with details is that in which *n*-pentyl chloride was reacted with ethyl 5-bromo-2-furoate.[109] The product was reported to have a 12° boiling range and attempted purification by redistillation was ineffectual. It is not unlikely, therefore, that a mixture[p] of alkylated products was obtained, containing an undetermined proportion of butylated ester. Saponification of

[p] Spectroscopic examination of the reaction mixture should be helpful in clearing up this point.

[145] Ipatieff, Pines and Schmerling, *J. Org. Chem.*, **5**, 253 (1940).

the impure product and sublimation of the acid was resorted to, and identification of the latter as 5-bromo-4-*t*-butyl-2-furoic acid was "by the method of mixed melting point determinations" although no melting point is listed. Presumably the "authentic" acid was that reported by Gilman and Burtner[144] who alkylated with *t*-butyl chloride and as mentioned previously obtained a very low product yield, which they attributed to steric influences. Under the circumstances additional work is warranted. It is regrettable that the *s*-butylated isomer, 5-bromo-4-*s*-butyl-2-furoic acid, has not been synthesized to date so that its behavior might be compared with the product of alkylation.

The alkylation reactions which have been discussed were carried out in carbon disulfide at room temperature with aluminum chloride as the condensing agent. *Sym*-tetrachloroethane was also found to be an effective solvent, whereas no alkylation took place when the reaction was conducted in nitrobenzene, in kerosene, or with no added solvent. When chlorobenzene was employed, ethyl 5-bromo-2-furoate was recovered unchanged, and a mixture of alkylated chlorobenzenes was obtained showing that this solvent is more susceptible to substitution than the beta positions of the bromo-furoic ester. The order of addition of the reagents appeared to be without effect, but it was found that at least one molecular equivalent of aluminum chloride was required for any alkylation to occur, and two molecular equivalents were actually used.[109]

Gilman and Turck[109] considered the possibility that destructive alkylation might be responsible for the apparently invariable introduction of a *t*-butyl radical by alkylating agents C_5 or higher; that the butyl group so introduced had its origin in the four-carbon furan nucleus. However, blank runs under the conditions of alkylation, but without the alkyl halide, permitted almost quantitative recovery of ethyl 5-bromo-2-furoate, or the corresponding acid. Furthermore, in several alkylation experiments it was possible to account for almost all of the original bromofuroic ester as alkylated product plus unchanged material. Thus the butyl radical must arise by degradation of the particular alkylating agent employed.

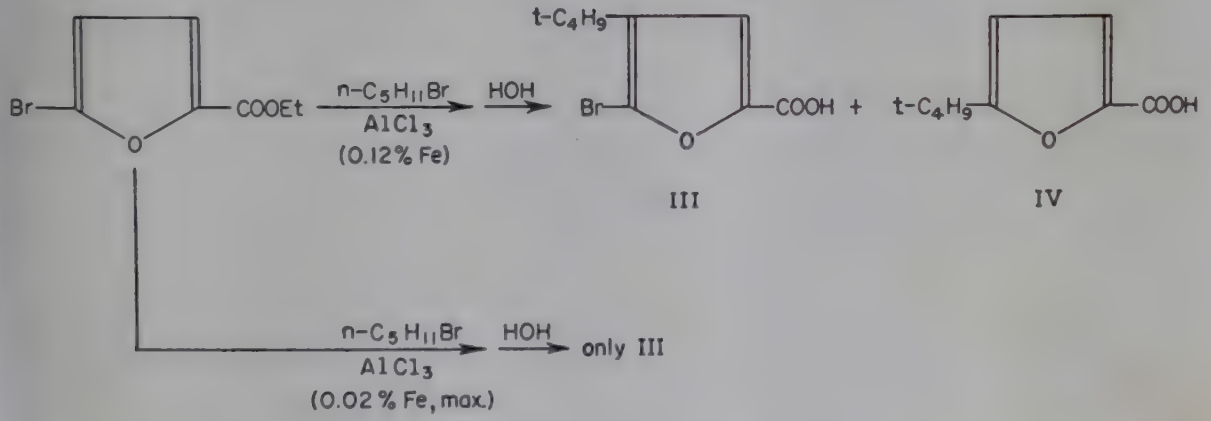
It was also considered that the nuclear bromine atom of ethyl 5-bromo-2-furoate might have sterically hindered the introduction of alkyl radicals of more than four carbon atoms.[q] Accordingly, the corresponding chloro ester was reacted with *n*-pentyl chloride to ascertain whether or not the smaller chlorine atom would permit substitution by a pentyl radical. Degradation of the alkylating agent took place as before; a butyl radical was introduced. The product so obtained was identical to that resulting when *t*-butyl bromide was condensed with ethyl 5-chloro-2-furoate, but no yield

[q] It is difficult to imagine how the *tert.*-butyl group could enter a hindered position more readily than, say, a *n*-pentyl group.

was reported in either instance.[109] Nevertheless, it would appear that the halogen atom of the halofuroic esters has an influence on the course of alkylation. No degradation of pentyl or hexyl halides to *t*-butyl was observed in the very comparable alkylation of methyl 2-furoate, C_5 and C_6 radicals, respectively, being introduced in reasonably high yield.[146]

In order to determine if the degradation and rearrangement of the alkyl halide was limited to beta substitution of furan compounds, *n*-pentyl chloride was condensed with ethyl 4-bromo-2-furoate in which there is an unsubstituted alpha position. Again degradation was observed, but in addition, the nuclear bromine atom was removed, and ethyl 5-*t*-butyl-2-furoate was obtained along with two acidic products which were not identified.[109] Since ethyl 2-furoate alkylates without degradation of the alkyl halide it would appear that, in the preceding reaction, the bromine atom was removed following alkylation and not before.

An unusual replacement-alkylation was observed on treating ethyl 5-bromo-2-furoate with *n*-pentyl bromide. A mixture of 5-bromo-4-*t*-butyl-2-furoic acid, III, and 5-*t*-butyl-2-furoic acid, IV, was obtained, indicating that a cleavage-rearrangement of the alkyl radical had occurred as before, but that in addition, the butyl radical had, to some extent, replaced the nuclear bromine atom. This behavior was subsequently traced to the aluminum chloride catalyst. Use of a resublimed grade, containing 0.02 per cent max. of iron gave only the alkylated bromo acid. When ferric chloride was added to bring the iron content of the aluminum chloride up to 0.12 per cent, a mixture of the two acids was again obtained.[109, 147]



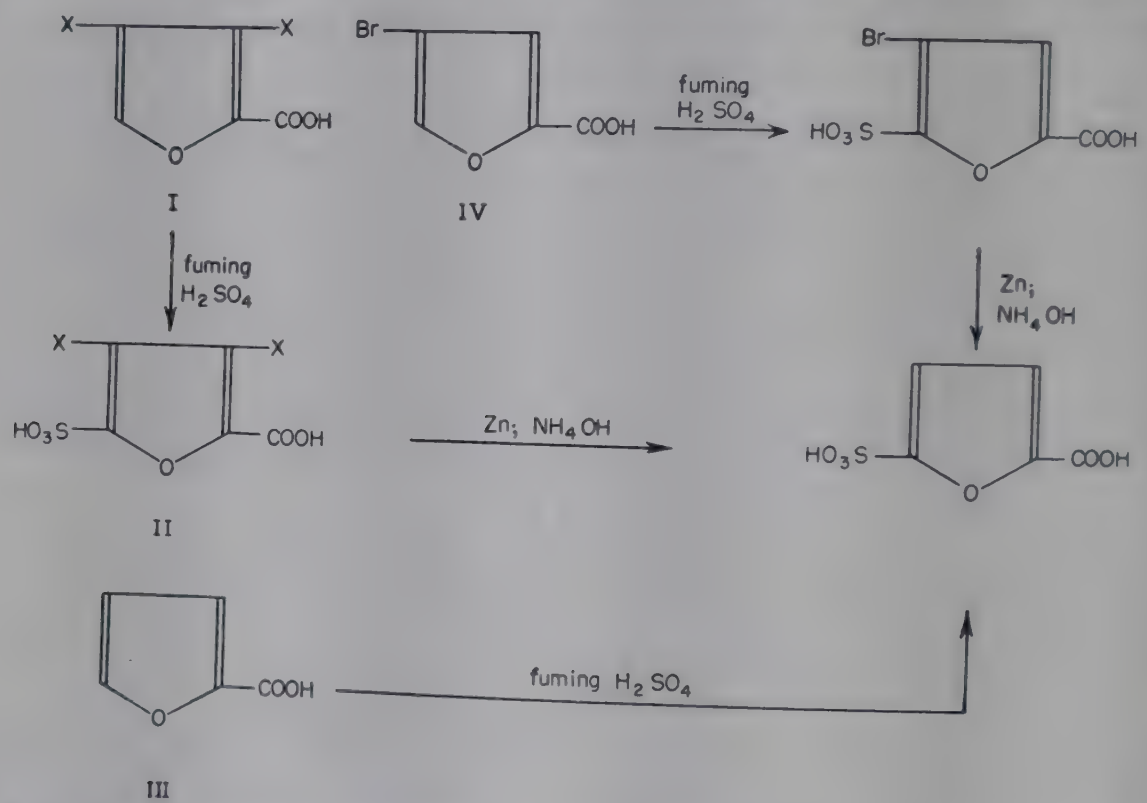
Ethyl 4,5-dibromo-2-furoate was recovered unchanged when alkylation was attempted in carbon disulfide with various alkyl halides and aluminum chloride. There was no evidence of reaction with *i*-propyl chloride even on refluxing for several hours.[109]

[146] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).

[147] McCorkle and Turck, *Proc. Iowa Acad. Sci.*, **43**, 205 (1936); *C. A.*, **32**, 4161 (1938).

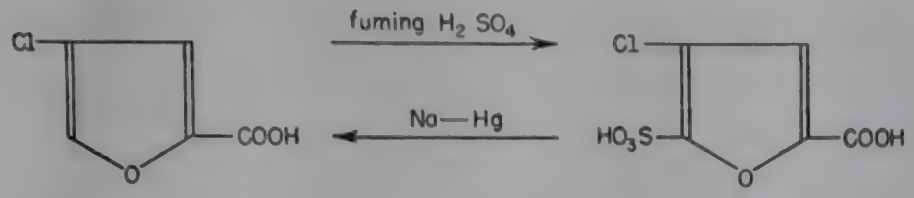
Sulfonation. Hill and co-workers sulfonated a number of halofuroic acids.[148, 149, 150, 151, 143, 152] No melting points were given for the sulfonic acids obtained, but several metal salts of each were described, including solubility data. The latter are of interest inasmuch as this was apparently the only means by which Hill was able to characterize the sulfo acids.

3,4-Dibromo- and 3,4-dichloro-2-furoic acids, I, dissolve without charring in fuming sulfuric acid and, on standing, the corresponding 3,4-dihalo-5-sulfo-2-furoic acids, II, are formed. In these two instances there can be no question of the location of the sulfo group, a point which Hill utilized in establishing the orientation on sulfonation of 2-furoic acid, III, and 4-bromo-2-furoic acid, IV. In these instances substitution takes place at the 5-position as demonstrated by the reactions illustrated below, wherein the same sulfo-2-furoic acid is obtained by three separate syntheses.



A similar attempt was made to fix the position of the sulfo group in the product (VI) obtained by sulfonation of 4-chloro-2-furoic acid, V. The chlorine atom was found to be firmly attached, however, and could not be eliminated by the action of zinc and ammonia. Quite unexpectedly, it was observed that treatment with sodium amalgam removes the sulfo group with regeneration of V. Subsequently it was observed that the sulfo group

[148] Hill and Palmer, *Proc. Am. Acad. Arts Sci.*, **23**, 188 (1887).
[149] Hill and Palmer, *Am. Chem. J.*, **10**, 373 (1888).
[150] Hill and Palmer, *Am. Chem. J.*, **10**, 409 (1888).
[151] Hill and Hendrickson, *Proc. Am. Acad. Arts Sci.*, **25**, 283 (1889).
[152] Hill and Sylvester, *Am. Chem. J.*, **32**, 185 (1904).

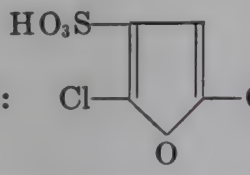


V VI

of 5-sulfo-2-furoic acid is similarly replaceable by hydrogen, whereas β-sulfo-furoic acids are resistant to attack by sodium amalgam. Hill offered this finding as evidence that the sulfo group of VI is attached to the number 5 nuclear carbon atom.

β-Sulfo-5-halo-2-furoic acids are obtained by dissolving 5-bromo- and 5-chloro-2-furoic acids in fuming sulfuric acid and permitting the reaction mixture to stand for several hours. The location of the sulfo group has not been established unequivocally, although Hill (see also [153]) assigned it to the 3-position in each instance. Both products are converted into the same β-sulfo-2-furoic acid when reduced with ammoniacal zinc dust, as indicated by comparison of the barium salts. That the sulfo group is more correctly assigned to the 4-position is indicated by later work whereby fusion of the β-sulfo-2-furoic acid with sodium formate gave rise to the known 2,4-furandicarboxylic acid.[154] This proof of orientation is predicated on the assumption that fusion of sulfonic acids or their salts with sodium formate does not involve rearrangement.

4-Sulfo-5-chloro-2-furoic acid:



The diamide, m.p. 212°; soluble in water and alcohol; insoluble in chloroform, ether, carbon disulfide and benzene; by the action of ammonia on the dichloride, obtained by treatment of the dipotassium salt with phosphorus pentachloride.[152] 4-Sulfamido-5-chloro-2-furoic acid, m.p. 194–195°; solubility characteristics similar to those of the diamide; by treatment of the diamide with barium hydroxide.[152]

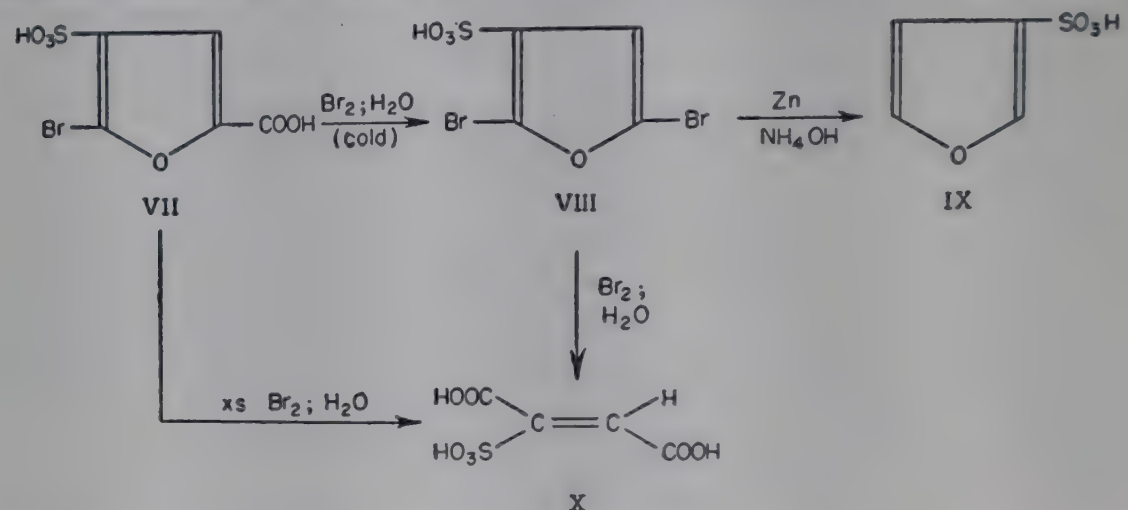
4-Sulfo-5-bromo-2-furoic acid: the diamide, m.p. 219–220°; obtained as in preceding example, but using phosphorus pentabromide. 4-Sulfamido-5-bromo-2-furoic acid, m.p. 190–191°.[152]

Fuming sulfuric acid does not sulfonate either 4,5-dibromo- or 4,5-dichloro-2-furoic acids. Instead, slow decomposition takes place with formation of bromo- and chloromaleic acids. Thus, the open beta position of the 4,5-dihalo acids is resistant to substitution by the sulfonic acid group just as it is to the introduction of bromine (see p. 111).

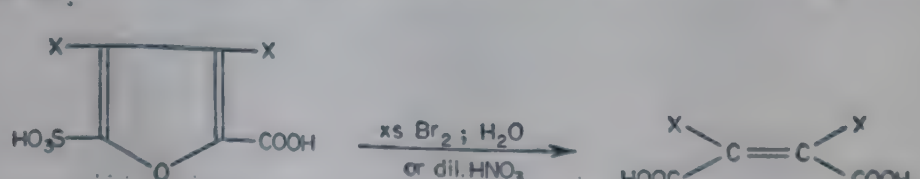
[153] Cinneide, *Nature*, **160**, 260 (1947).
[154] Gilman, Calloway and Smith, *J. Am. Chem. Soc.*, **56**, 220 (1934).

On the other hand, the beta hydrogen atom of 3,5-dichloro-2-furoic acid appears to be capable of replacement since Hill and Jackson[32] report a dichlorosulfofuroic acid by the action of fuming sulfuric acid. Few details of the product are given, but the barium salt gave the correct analysis.

The behavior of the sulfohalo-2-furoic acids on oxidation is similar to that discussed previously for the nonsulfonated acids. For example, by slow addition of one mole of aqueous bromine, in the cold, reaction may be confined essentially to replacement-decarboxylation, whereas an excess of reagent effects more complete oxidation to derivatives of maleic or fumaric acids. This is illustrated below for the specific case of β-sulfo-5-bromo-2-furoic acid, VII[149] (see also [151, 152]). Cinneide[153] applied the former reaction condition to obtain 2,5-dibromo-3-furansulfonic acid, VIII, from



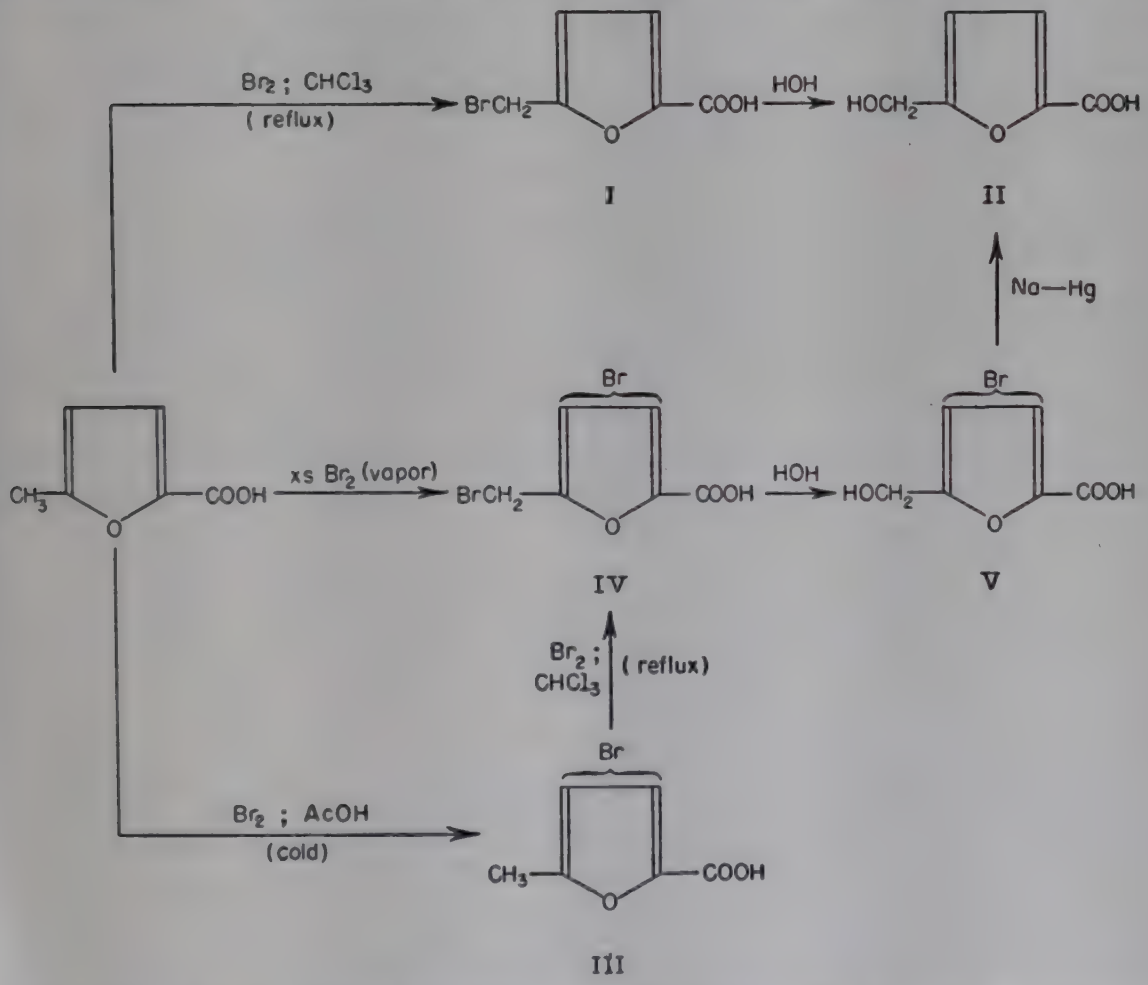
which he was successful in obtaining 3-furansulfonic acid, IX, by the action of zinc and ammonia. The structure of VIII, which is obtained in nearly theoretical yield, is not in doubt by analogy with the formation of 2,5-dibromofuran from 5-bromo-2-furoic acid under similar conditions.[3] The identity of the sulfofumaric acid, X, obtained by oxidative cleavage of VII and VIII, is reasonably well substantiated, although the many analyses of its salts[148, 149, 150] do not check as well as might be hoped. More recently, however, it has been shown[155] that the same product may be obtained by direct sulfonation of maleic and fumaric acids. It would appear, therefore, that a sulfo group attached to a beta position of the furan nucleus is retained in the oxidation product; it will be recalled that β-halogen substituents are similarly retained. A sulfo group attached to an alpha nuclear carbon atom, however, is eliminated under similar oxidizing conditions[148, 149, 150, 143, 151]:



[155] Backer and Van der Zanden, *Rec. trav. chim.*, **49**, 735 (1930).

Homologous Halo-2-furoic Acids

The direct bromination of 5-methyl-2-furoic acid was studied by Hill and Jennings[156] who suggest that the nature of the products formed (lateral vs. nuclear bromination) is dependent upon the temperature of reaction. Thus, when reaction with bromine is carried out in boiling chloroform a bromo acid, I, is obtained which is readily hydrolyzed in aqueous medium to a compound analyzing correctly for (hydroxymethyl)furoic acid, II. On the other hand, by conducting the reaction in glacial acetic acid below 17°, substitution is confined to the nucleus with the formation of 5-methyl-4(or 3)-bromo-2-furoic acid, III. The further action of bromine on the latter, in boiling chloroform, introduces a second bromine atom. The dibromo acid (IV, m.p. 175°, (dec.)) so obtained hydrolyzes readily with formation of a (hydroxymethyl)bromofuroic acid, V, which is reduced by sodium amalgam to II. IV is also formed by extended (12–16 hours) exposure of 5-methyl-2-furoic acid to an excess of bromine vapor at room temperature. The semi-liquid product first formed was worked up and



recrystallized from boiling toluene. Hill concluded that, at low temperature, bromine first attacks the nucleus and then the methyl group, whereas at

[156] Hill and Jennings, *Am. Chem. J.*, **15**, 158 (1893).

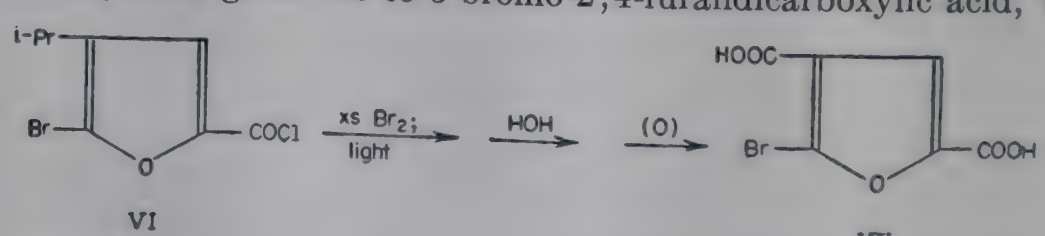
elevated temperatures, the side chain is the first point of attack although some nuclear substitution may occur simultaneously.

The only other nuclear halogenated alkyl-2-furoic acid which has been prepared by direct halogenation is the 5-bromo-4-*i*-propyl acid. The conditions of bromination of the original isopropylfuroic acid were not described, but the product was identical to that obtained (a) by oxidation of 5-bromo-4-*i*-propylfurfural or (b) by hydrolysis of the ester obtained by alkylation of ethyl 5-bromo-2-furoate with *i*-propyl chloride.[107, 108] The remaining acids of this classification which have been reported were obtained by alkylation of the appropriate ethyl 5-halo-2-furoate and subsequent hydrolysis.

TABLE 8. ALKYLHALO-2-FUROIC ACIDS

Substituted 2-furoic acid	M.p. (°C.)	Derivatives (°C.)	Ref.
4(or 3)-Bromo-5-methyl	150–151	—	156
5-Bromo-4-*i*-propyl	103–104	ethyl ester, b.p. 141–144 (17 mm.) n_D^{25} 1.5072	108
		acid chloride, b.p. 129–131 (15 mm.)	
5-Bromo-4-*t*-butyl	164	ethyl ester, b.p. *ca.* 152 (13 mm.)	144
5-Chloro-4-*t*-butyl	172–173	—	109

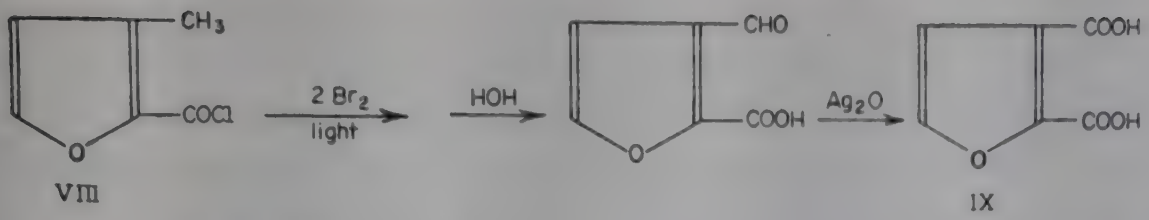
5-Bromo-4-*i*-propyl-2-furoic acid was converted into the acid chloride (VI) in 85 per cent yield using thionyl chloride. When the latter, illuminated by a Corex mercury vapor lamp, was treated at 125–140° with an excess of bromine, hydrogen bromide was evolved. This reaction proceeds via polybromination of the *i*-propyl group. Thus, hydrolysis of the product, and subsequent oxidation with alkaline silver oxide, and finally with potassium ferricyanide gives rise to 5-bromo-2,4-furandicarboxylic acid, VII.[108]



VI VII

In the preceding experiment, substitution of the side chain occurred in preference to replacement of an α-nuclear hydrogen atom. A similar result was observed by Asahina in his work with 3-methyl-2-furoyl chloride, VIII, which also possesses an open alpha position. Treatment of VIII at 130° in direct sunlight with two moles of bromine gave, on subsequent hydrolysis, an aldehyde acid which was oxidized by silver oxide to 2,3-furandicarboxylic acid, IX.[157] This experiment indicates that substitution was confined to the methyl substituent. Some nuclear bromination may

[157] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta Phytochim.*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).



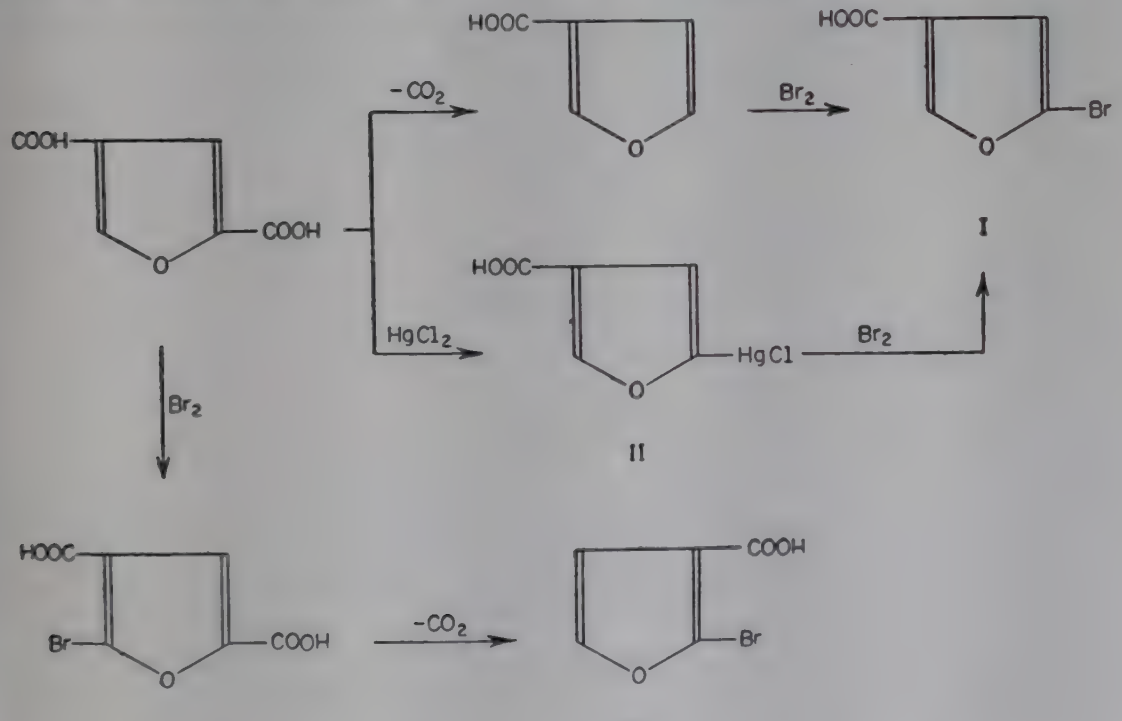
VIII IX

have occurred simultaneously, however, in view of the results reported by Asahina[157] when the isomeric 2-methyl-3-furoyl chloride was treated under similar conditions (see p. 132).

From the meager information at hand it would appear that, as is true in the benzene series, exposure to light promotes side chain substitution of the alkylfuroic acids. Further reference to this is made in the section which follows.

Halo-3-furoic Acids and Homologs

Two of the three isomeric bromo-3-furoic acids have been synthesized. One of these, 5-bromo-3-furoic acid, I (m.p. 130°), was obtained in 32 per cent yield by the direct action of bromine at 5°, on 3-furoic acid in chloroform.[130] It has also been obtained by fission of the appropriate mercurial (II) with bromine.[130] Thus the directing influence of the carboxyl group of 3-furoic acid is established. An entering bromine atom orients to the alpha position farthest removed from the carboxyl.



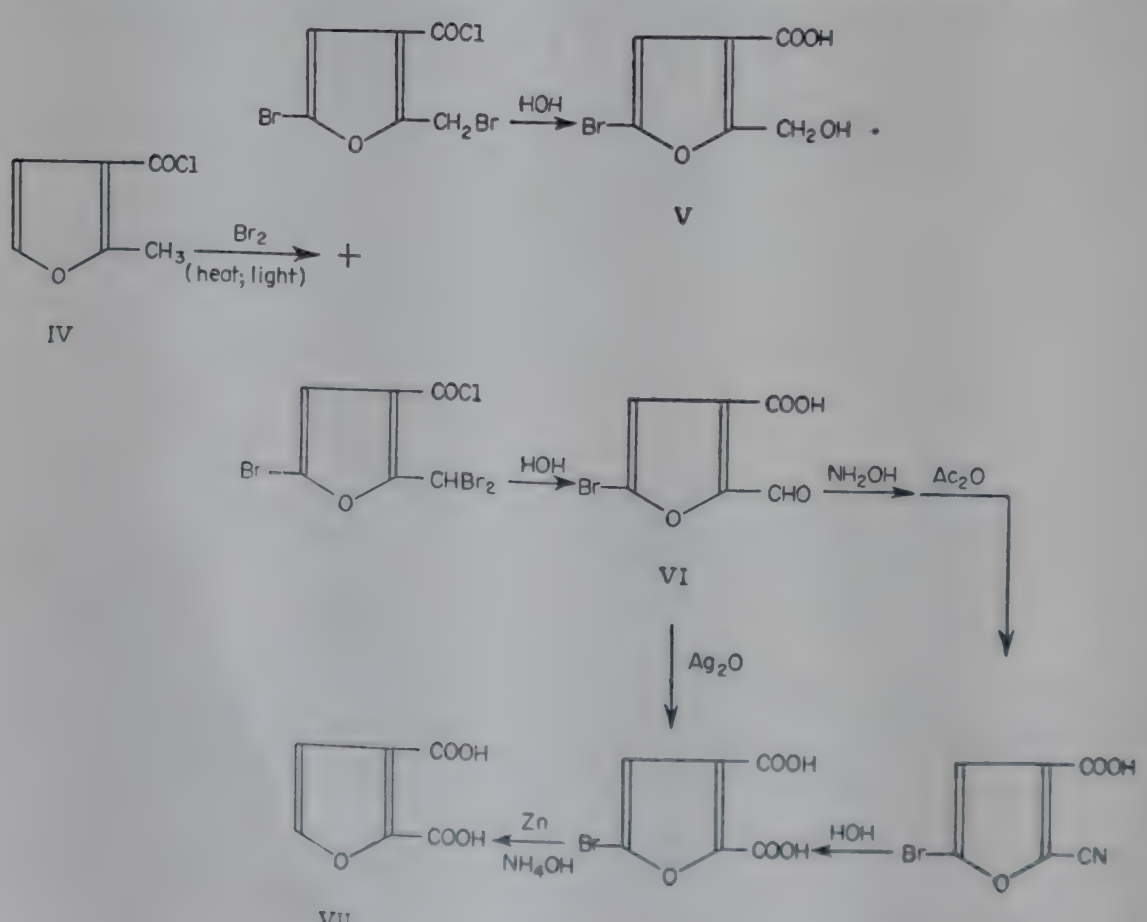
The other known isomer, 2-bromo-3-furoic acid, III (m.p. 158°), was obtained by selective decarboxylation of 5-bromo-2,4-furandicarboxylic acid.[130] The corresponding chloro acids have not been reported, nor are any di- or trihalo-3-furoic acids known.

The action of halogens on alkyl-3-furoic acids may result in substitution on either the nucleus or side chain or both, although the conditions affect-

ing the relative extent to which each occurs are less well defined than in the benzene series. Exposure to sunlight appears to promote substitution in the side chain. The nature of the reaction medium may also influence the direction. This is indicated in part by the work which has been reported on the reaction of chlorine and bromine with 2-methyl-3-furoic acid.

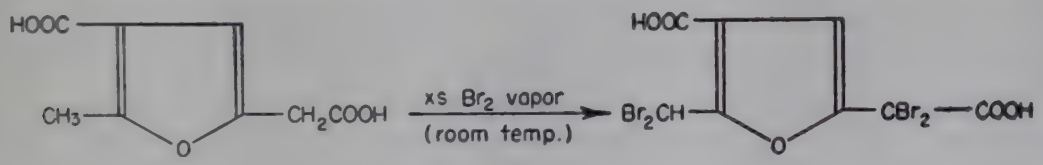
No chlorination of the methyl group occurs when ethyl 2-methyl-3-furoate is treated, at 145°, with somewhat less than one mole of dry chlorine. Saponification of the reaction mixture gives rise to 5-chloro-2-methyl-3-furoic acid as the only isolable product.[39] Similarly, the corresponding 5-bromo acid is the sole product reported by reaction of bromine with 2-methyl-3-furoic acid at 5°.[158]

On the other hand, treatment of 2-methyl-3-furoyl chloride (IV) at 130° with approximately two moles of bromine in direct sunlight, gives evidence of combined nuclear and side chain bromination[157] (compare 3-methyl-2-furoyl chloride, p. 130). Subsequent hydrolysis of the reaction mixture yields a compound which analyzes correctly for a bromo-(hydroxymethyl)furoic acid, V (m.p. 116°). Remaining in the mother liquor is a compound (presumably VI) which is transformed into 2,3-furandicarboxylic acid, VII, by oxidation with silver oxide and subsequent reduction with zinc and ammonia. The aldehydic nature of VI is shown by its conversion to an oxime which was dehydrated to the corresponding bromo nitrilo acid. Saponification of the latter gave rise to a bromo-2,3-furandicarboxylic acid which, following reduction, was converted into VII.



The position of the nuclear bromine atom in these several compounds is not known with certainty. It has been assigned to the 5- rather than the 4-position, since introduction of a halogen into the furan ring always occurs preferentially at an alpha carbon. From the data at hand, it is not possible to discern whether nuclear and side chain substitution occurs simultaneously or separately. If the validity of locating the nuclear bromine atom at the 5-position be assumed, however, it is clear that replacement of a hydrogen atom in the side chain takes place in preference to nuclear substitution of IV at the open beta (4-) position.

On the other hand, Gilman and Burtner[159] report beta-nuclear bromination of 2,5-dimethyl-3-furoic acid with no mention of attack on the methyl groups. The reaction, which carried out in glacial acetic acid at 5°, using 1.5 molar equivalents of bromine, gave rise to 4-bromo-2,5-dimethyl-3-furoic acid. Many years earlier, Dietrich and Paal[160] (see also [161]) had exposed 2,5-dimethyl-3-furoic acid to dry bromine vapor at 15°, in the absence of a solvent, and reported the formation of a tetrabromo substitution product, $C_7H_4Br_4O_3$ (m.p. 161–162°), in almost quantitative yield. The location of the bromine atoms was not definitely established, but their removal by the action of sodium hydroxide, indicates their attachment to the methyl groups. A similar result has also been reported by Trefil'ev,[162, 163] who exposed the related methronic acid, VIII, to bromine vapor at room temperature for several weeks, and obtained a tetrabromo substitution product. Under the same conditions methylmethronic acid (2,4-dimethyl-5-carboxymethyl-3-furoic acid), which has no unsubstituted nuclear carbon atom, was likewise substituted by four atoms of bromine. On the other hand,



VIII

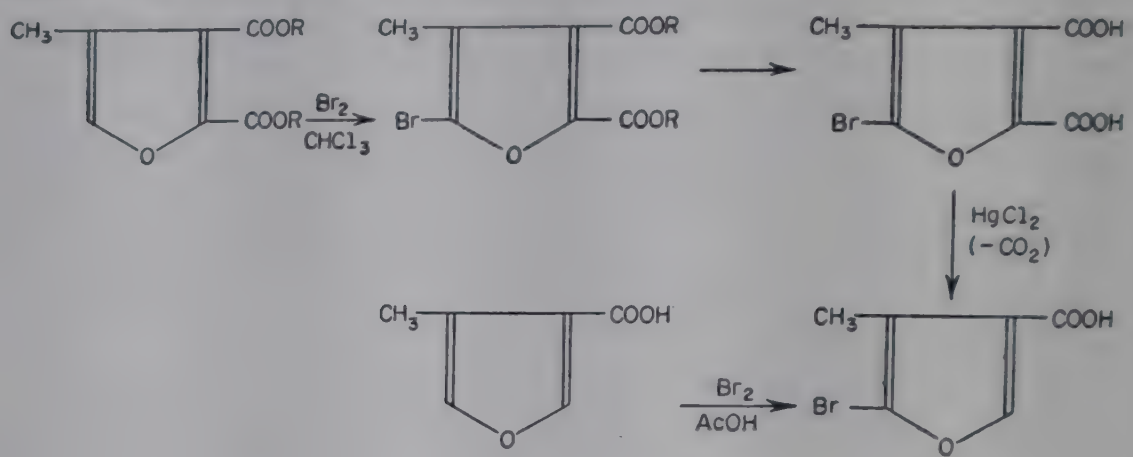
dibromo compounds were obtained by similar treatment of 4-methyl-2-carboxymethyl-3-furoic acid (isomer of VIII, wherein the methyl group is attached to a β-nuclear carbon), and 2-phenyl-5-carboxymethyl-3-furoic acid. Trefil'ev concluded that substitution of these furan types by bromine, in the absence of a solvent, is confined to aliphatic side chains; that under the conditions employed, only such groups located on an α-nuclear carbon are involved. His formulation of the reaction with VIII is outlined above.

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[158] Gilman, Burtner and Smith, *Rec. trav. chim.*, **51**, 407 (1932).
[159] Gilman and Burtner, *Rec. trav. chim.*, **51**, 667 (1932).
[160] Dietrich and Paal, *Ber.*, **20**, 1077 (1887).
[161] Böttinger, *Ber.*, **17**, 317 (1884).
[162] Trefil'ev, *Ber.*, **40**, 4388 (1907).
[163] Trefil'ev, *J. Russ. Phys. Chem. Soc.*, **40**, 1341 (1908); *C. A.*, **3**, 636 (1909).

It must be borne in mind, however, that the structure of the product has not been definitely established.

From 4-methyl-3-furoic acid in acetic acid at 15–20°, Gilman and Burtner[164] obtained the corresponding 5-bromo acid, IX, by incremental addition of somewhat more than one molecular equivalent of bromine. The orientation is known by the sequence of reactions outlined below.



IX

5-Chloro-2-methyl-3-furoic acid: m.p. 122–123°. Prepared by the action of dry chlorine on ethyl 2-methyl-3-furoate at 145°. The reaction was stopped when the gain in weight attained 80–90 per cent of the amount calculated for the introduction of one chlorine atom. Saponification gave the chloro acid in 35–50 per cent yield.[39]

5-Bromo-2-methyl-3-furoic acid: m.p. 118°. Obtained in 22 per cent yield by dropwise addition of bromine to 2-methyl-3-furoic acid at 5°, and allowing the mixture to stand at room temperature overnight.[158]

5-Bromo-4-methyl-3-furoic acid: m.p. 163–164°, 165°. For preparation, see text.[164]

4,5-Dibromo-2-methyl-3-furoic acid: m.p. 186–189°. Synthesis involved reaction of bromine in carbon tetrachloride with ethyl 4,5-bis(chloromercuri)-2-methyl-3-furoate followed by hydrolysis to the desired acid.[127]

5-Bromo-2,4-dimethyl-3-furoic acid: m.p. 154° (dec.). Formed in 71 per cent yield by dropwise addition of bromine (1.5 moles) at 5° into 2,4-dimethyl-3-furoic acid (1 mole) in glacial acetic acid.[159]

4-Bromo-2,5-dimethyl-3-furoic acid: m.p. 181° (dec.). Synthesis (33 per cent yield) as in the preceding preparation using 2,5-dimethyl-3-furoic acid.[159]

4-Iodo-2,5-dimethyl-3-furoic acid: m.p. 208.8°. Prepared from 3,4-diiodo-2,5-dimethylfuran by treatment with methylmagnesium iodide and subsequent carbonation.[41]

Halofurandicarboxylic Acids and Homologs

As might be expected, the introduction of a halogen atom into the nucleus of 2,5-furandicarboxylic acid by the direct action of bromine or chlorine requires forced conditions. As a matter of fact, Klinkhardt[165] and

[164] Gilman and Burtner, *J. Am. Chem. Soc.*, **71**, 1213 (1949).
[165] Klinkhardt, *J. prakt. Chem.*, **25**, 41 (1882).

Phelps and Hale[18] were unsuccessful in their attempts to brominate this compound. Klinkardt did obtain a dark brown, oily liquid on heating the acid with bromine in a sealed tube; possibly a di- or tetrabromo addition product. On standing, the oil evolved bromine, and regenerated the original acid. It was not analyzed, nor was it examined further. Later, Hill[166] observed that the acid chloride, 2,5-$C_4H_2O(COCl)_2$, was resistant to bromine at temperatures as high as 250°. Neither was reaction achieved by exposing the reactants to direct sunlight or by using aluminum bromide and phosphorus bromide under a variety of conditions.

The use of chlorine with the diethyl ester was more successful.[135] Extended heating at a maximum of 100°, results in the addition of four atoms of chlorine, and some substitution as indicated by analysis. By the action of alcoholic sodium hydroxide on the viscous, oily reaction product, there is obtained 3,4-dichloro-2,5-furandicarboxylic acid.

By virtue of its unsubstituted alpha position, 2,4-furandicarboxylic acid is somewhat more susceptible to halogenation than the 2,5-dicarboxylic acid. Heating the dimethyl ester with bromine at 160°, for eight hours effects substitution at the 5-position with formation of 5-bromo-2,4-furandicarboxylic acid.[130]

Nothing has been reported on the direct halogenation of the 3,4- or 2,3-furandicarboxylic acids. In relation to the former, however, Trefil'ev[167] (see also [168]) reports the formation of tetrabromo addition products by the action of bromine in carbon disulfide on the mono- and diethyl esters of the homologous 2,5-dimethyl-3,4-furandicarboxylic acid. The tetrabromides were very unstable and decomposed spontaneously. By contrast, Gilman and Burtner[164] obtained 5-bromo-4-methyl-2,3-furandicarboxylic ester by treating the parent ester with bromine in chloroform at 20°. The other bromine substituted 2,3-furandicarboxylic acids which have been described (Table 9) were obtained by oxidation of the appropriate 2-methyl-3-furoic acids as discussed earlier (p. 132).

TABLE 9. HALOFURANDICARBOXYLIC ACIDS

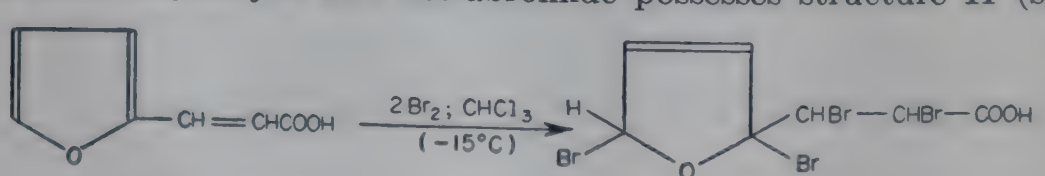
Substituted furan	M.p. (°C.)	Ref.
3,4-Dichloro-2,5-dicarboxy	297	135
	dimethyl ester, m.p. 157–158	
5-Bromo-2,4-dicarboxy	250	130
5-Bromo-2,3-dicarboxy	125 (crude)	157
4,5-Dibromo-2,3-dicarboxy	242–243	127
5-Bromo-4-methyl-2,3-dicarboxy	257 (dec.)	164
	dimethyl ester, m.p. 131–132	

[166] Hill, *Am. Chem. J.*, **25**, 439 (1901).
[167] Trefil'ev, *Ukrainski Khem. Zhur.*, **1**, Sci. Pt., 121 (1925); *C. A.*, 23, 3926 (1929).
[168] Trefil'ev, *Ber.*, **39**, 1863 (1906).

Halogenation of 3-(2-Furyl)acrylic Acid and Its Derivatives

No information is available on the chlorination of 3-(2-furyl)acrylic acid, but the action of bromine on this acid and its derivatives has been studied. As expected, both the nucleus and the side chain are attacked by bromine. The evidence indicates that reaction occurs stepwise, and that the initial step may be addition to the nucleus. Thus, under selected conditions, it has been possible to limit bromination to the furan ring, whereas no technique has yet been described which confines the reaction to the olefinic side chain. Accordingly, it would appear that the unsaturated furan system is more reactive than the olefinic double bond, a consequence, no doubt, of the deactivating effect of the carboxyl group on the latter. The more reactive ethylenic bond of vinylfuran permits preliminary addition of bromine to give, at least in part, the dibromide $C_4H_3O—CHBr—CH_2Br$,[87] although it is not improbable that, in this instance some nuclear brominated products are also formed.

Moureu, Dufraisse and Johnson[169] attempted without success to prepare 2,3-dibromo-3-(2-furyl)propionic acid by treating furylacrylic acid, I, with bromine at −15° in chloroform. Under these conditions, they obtained a crystalline, tetrabromo addition compound (m.p. 110–111° (dec.)) irrespective of whether one or two molecular equivalents of bromine were employed. In the former instance, half of the original furylacrylic was unattacked and recoverable. The action of mercury[169] or zinc dust[2] on the tetrabromide removes the halogens with regeneration of I. Stripping the bromine atoms is also achieved by the action of either sodium carbonate or sodium sulfite, but under these conditions, it has not been possible to isolate simple reaction products. It was suggested that two of the bromine atoms in the tetrabromide were located on the side chain, and that the remaining two were linked to the nuclear oxygen atom in the form of an oxonium complex.[169] As pointed out by Clauson-Kaas,[5] however, addition of bromine to carbon atoms 2 and 5 of the furan ring is more probable on which basis furylacrylic acid tetrabromide possesses structure II (see [2]).



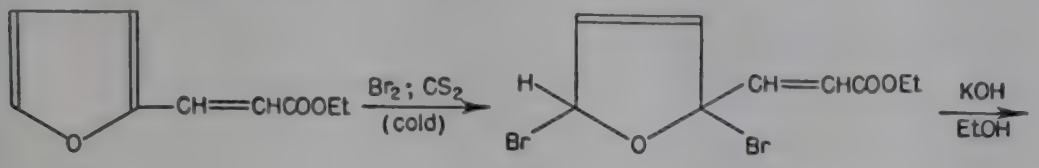
I II

Similarly avoiding elevated temperatures, Gilman and Wright[1] successfully isolated a dibromo addition compound, m.p. 60°,[r] by treatment

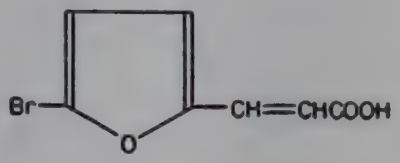
[r] When crystallized at low temperature from petroleum ether, the dibromide melted at 70°[21] (see also [2]).

[169] Moureu, Dufraisse and Johnson, *Ann. chim.* (*10*), **7**, 5 (1927).

of ethyl furylacrylate in carbon disulfide with one mole of bromine. The action of zinc dust on an alcoholic solution of the dibromide removes the bromine atoms, whereas mercury appears to have no effect. With alcoholic potassium hydroxide, however, the dibromide gives rise to 3-(5-bromo-2-furyl)acrylic acid, IV, the structure of which was established by separate synthesis from 5-bromofurfural.[170] Accordingly, one of the bromine atoms of the dibromide is attached to the nucleus at position 5, and while the location of the other has not been established unequivocally, Gilman and Wright favored structure III.



III



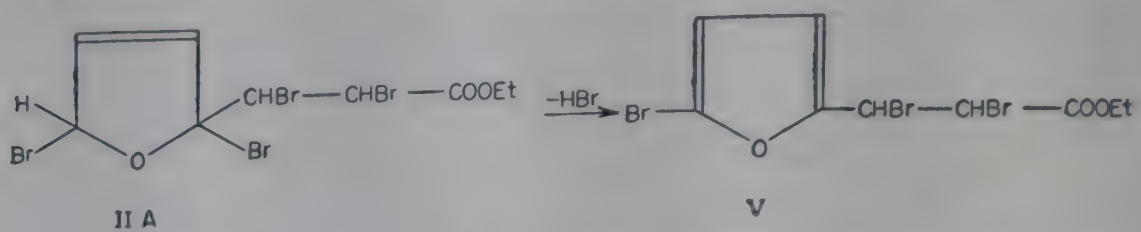
IV

The tetrabromo and dibromo addition compounds which have been described are very unstable, and decompose readily even at room temperature with elimination of hydrogen bromide, probably by 1,4-type elimination from the nucleus. Thus spontaneous decomposition of III, and subsequent hydrolysis, gives a low yield of IV.[1] Similarly, II has been shown to decompose on standing with formation of the dibromo ester, V.[2] Dehydrobromination is accelerated by the presence of boron bromide, and iodine, among others.[2]

Gilman and Wright[1] cited their work as supporting evidence for the view that substitution of aromatic types proceeds by a mechanism involving the preliminary formation of addition products. They did not observe the formation of any by-product tetrabromide in their synthesis of III, although in one instance they obtained, in addition to the latter, approximately an equal amount of a compound containing three atoms of bromine. The experimental conditions were the same as before, except that chloroform was used as the solvent, and following addition of the bromine, most of the chloroform was removed by distillation (under vacuum at room temperature) whereupon the reaction mass crystallized. The dibromide, III, was separated by dissolving in petroleum ether, leaving 2,3-dibromo-3-(5-bromo-2-furyl)acrylic ester, V. In view of what has gone before, it is reasonable to suppose that V had its origin in the ester tetrabromide,

[170] Gilman and Wright, *Rec. trav. chim.*, **49**, 195 (1930).

II A, although the latter was not isolated. That is, dehydrobromination of II A probably occurred during the step of removing the solvent.



II A V

In view of the instability of the bromo adducts it is not surprising that such compounds are not found if the temperature is permitted to rise during bromination of furylacrylic acid and its derivatives, or in the steps incident to product isolation. Instead, substitution products are obtained with a bromine atom attached to position 5 of the furan ring. As expected, the brominated side chain is more stable than the nuclear dibromide, although the former does undergo dehydrobromination at elevated temperatures.

The early work of Gibson and Kahnweiler[89, 90] involved slow addition of two moles of bromine to furylacrylic acid dissolved in carbon disulfide. Subsequently, the reaction mixture was heated for some time at approximately 50°. The product isolated was assigned the structure of 2,3-dibromo-3-(5-bromo-2-furyl)propionic acid, V A, although proof of the location of the nuclear bromine atom was not established until much later.[170] The action of zinc dust on an alcoholic solution of V A removes two atoms of bromine with the formation of 3-(5-bromo-2-furyl)acrylic acid, IV, which, in turn, reunites with bromine to regenerate V A.[89, 90, 2]

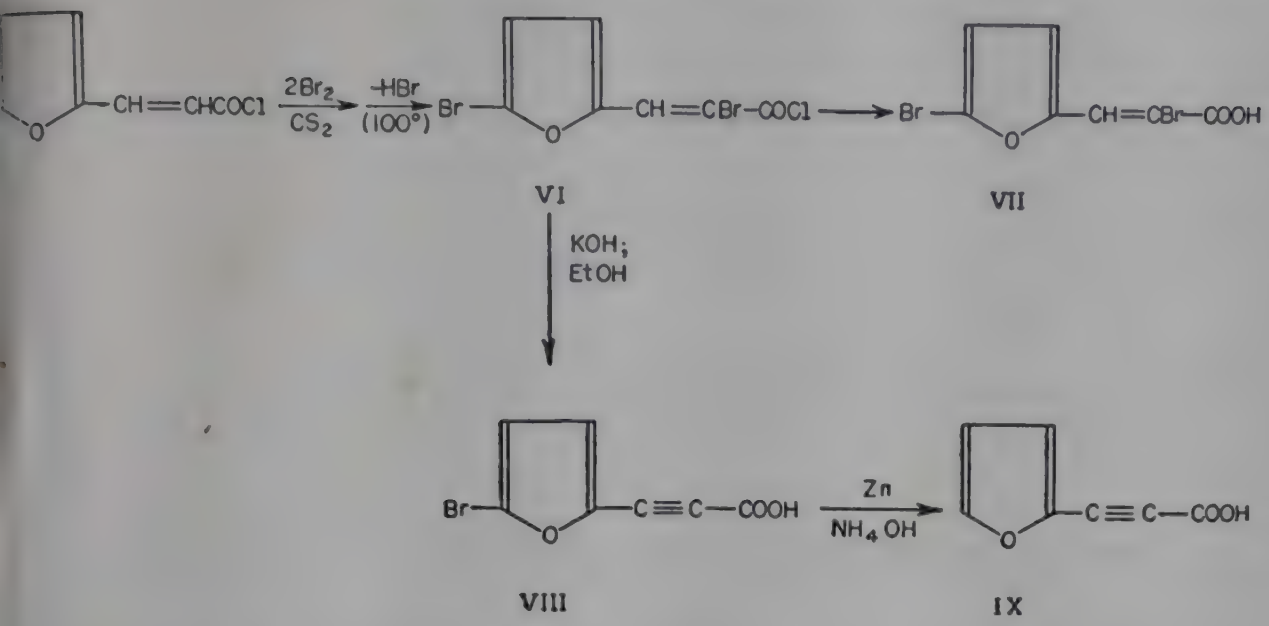
$$C_4H_3O—CH=CHCOOH \xrightarrow[\text{low temp.}]{2Br_2;\ CS_2} \xrightarrow{50°C.}$$

$$Br—C_4H_2O—CHBrCHBrCOOH \xleftarrow{Br_2} Br—C_4H_2O—CH=CHCOOH$$

VA IV

Using furylacrylyl chloride, Gilman and his associates[91] essentially duplicated the preceding bromination procedure, except that, following removal of the solvent, the reaction mixture was heated in vacuum at 100°. until evolution of hydrogen bromide ceased. 2-Bromo-3-(5-bromo-2-furyl)-acrylyl chloride, VI, was obtained in approximately 90 per cent yield, and converted, by way of the corresponding ethyl ester into the free acid, VII, the properties of which were identical to those of the acid obtained earlier[89, 90] by thermal (130°) dehydrobromination of V A.

Assignment of the lateral bromine atom to the carbon atom alpha to the carboxyl group rests solely on analogy with related benzene types.



Synthesis of 5-bromo-2-furylpropiolic acid, VIII, was successfully accomplished by elimination of hydrogen bromide from VII, using either dilute,[s] aqueous sodium hydroxide or preferably, alcoholic potassium hydroxide.[91] Reduction of VIII with zinc dust in ammonium hydroxide, removes the nuclear bromine atom to give 2-furylpropiolic acid, IX.[91] The conversion of these various compounds into derivatives of vinyl- and ethynylfuran is discussed elsewhere (p. 100).

By altering the experimental conditions, bromination of furylacrylyl chloride may be essentially confined to the nucleus. Thus 3-(5-bromo-2-furyl)acrylyl chloride was obtained in 56 per cent yield by dropwise addition of one mole of bromine to a cold solution of the starting material in carbon disulfide. The reaction mixture was held under reduced pressure for twenty-four hours, following which the residue was distilled *in vacuo*.[91]

Comparison of this reaction with that immediately preceding in which two moles of bromine were employed, shows that while both the nucleus and the side chain can be brominated, the reaction proceeds stepwise and in that order. An apparently opposite conclusion was reached by Bechert[171] who reported formation of C_4H_3O—CBr=C(CN)—COOEt by bromination of ethyl 2-cyano-3-(2-furyl)acrylate in hot, glacial acetic acid. That the bromine atom actually entered the nucleus to form 2-cyano-3-(5-bromo-2-furyl)acrylic ester, X, was established by unequivocal synthesis; X was obtained as the product of the condensation of 5-bromofurfural with ethyl cyanoacetate.[172]

[s] With strong aqueous alkali, fission occurs, to some extent, with the formation of 5-bromo-2-furyl methyl ketone.[91]

[171] Bechert, *J. prakt. Chem.*, **50**, 16 (1894).

[172] Gilman and Young, *Rec. trav. chim.*, **51**, 761 (1932).

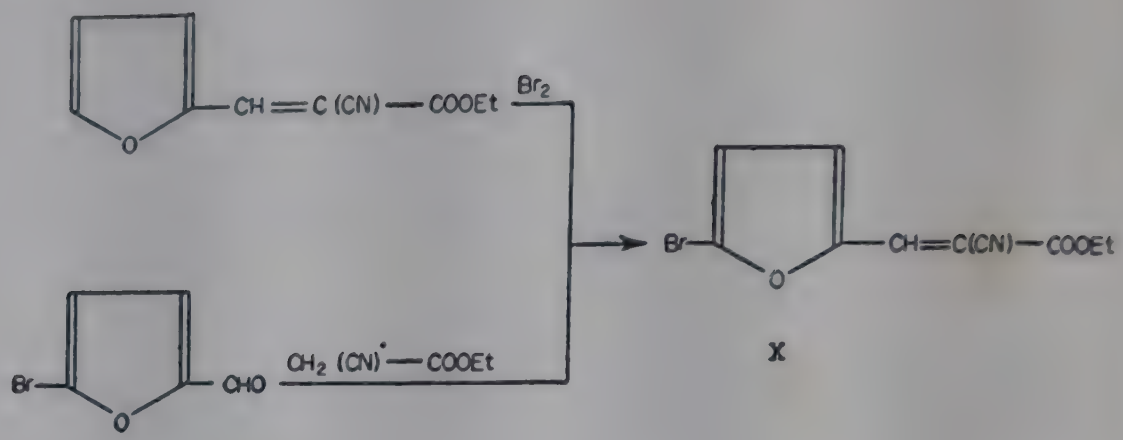


TABLE 10. (HALOFURYL)-ALKANOIC, -ALKENOIC AND -ALKYNOIC ACIDS

Acid	Structure	M.p. (°C.)	Derivatives (°C.)	Ref.
2,3-Dibromo-3-(5-bromo-2-furyl)propionic	V A	153.5–154	ethyl ester: m.p. 70	169, 1, 2
3-(5-Bromo-2-furyl)-acrylic	IV	174–175, 176–177	ethyl ester: m.p. 42 b.p. 151–152 (14 mm.) acid chloride: m.p. 54 b.p. 182–188 (crude)	89, 90, 91, 2
3-(5-Chloro-2-furyl)-acrylic	—	—	methyl ester: b.p. 98–100 (7 mm.)	102
2-Bromo-3-(5-bromo-2-furyl)acrylic	VII	178–179	ethyl ester: m.p. 55–56 acid chloride: m.p. 72 b.p. 182–183 (21 mm.)	89, 90, 91, 2
2-Cyano-3-(5-bromo-2-furyl)acrylic	X (Et = H)	—	ethyl ester: m.p. 110–111	172; see also 171
5-Bromo-2-furylpropiolic	VIII	143	α-naphthalide: m.p. 150	91

Chapter 4

NITRO COMPOUNDS OF THE FURAN SERIES

The scope of this chapter is such as to include all furan compounds which possess one or more nitro groups directly attached to the nucleus irrespective of the nature of other substituents. In addition, it was convenient to include here (p. 167) the furylnitroölefins and their laterally saturated relatives, the (nitroalkyl)furans.

The earliest reported nitro-substituted furan compounds were derived from furancarboxylic and furansulfonic acids[1, 2, 3] and from other stable furan types such as the products obtained by condensation of furfural with compounds possessing reactive methylene groups[4, 5]. In these instances nitration was effected directly using fuming nitric acid, and the products were isolated by dilution of the reaction mixture with water. Such treatment is too harsh, however, when applied to furan and many of its simple derivatives, which are largely destroyed under these conditions.

Marquis[6, 7, 8] was the first to successfully nitrate furan itself. This he accomplished by use of a mixture of nitric acid and acetic anhydride as the nitrating agent, a technique later adopted by Rinkes, Gilman, Johnson, and others (see also [9, 10]) for the nitration of a variety of furan derivatives. The work of these investigators has shown, in several instances, that α-nitration proceeds by way of an intermediate addition product from which the desired nitrofuran is subsequently derived by the action of a mild base. It is not improbable that α-nitration in the furan series always occurs in this way, although the intermediate has not been isolated in every case. The structure of the intermediate is that of a 2,5-dihydrofuran (p. 142) which is relatively unstable and, as in the case of the related halogen addition products (Chapter 3), susceptible to hydrolytic degradation.

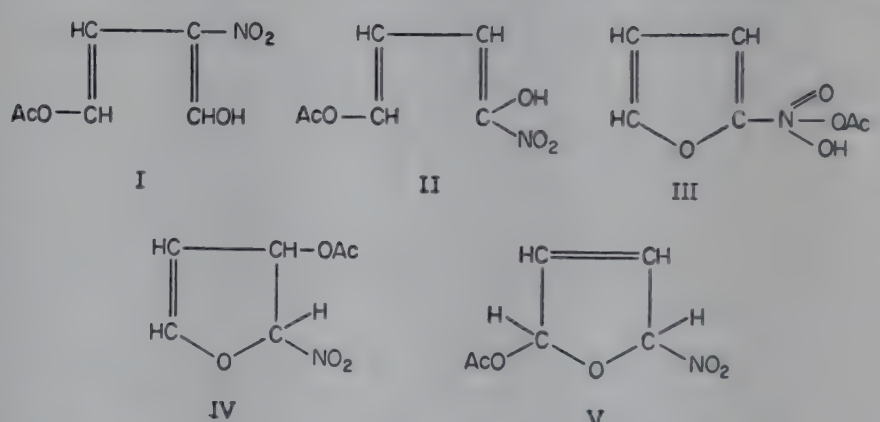
In recent years considerable interest has developed in nitrofuran com-

[1] Klinkhardt, *J. prakt. Chem.*, **25**, 41 (1882).
[2] Hill and Palmer, *Proc. Am. Acad. Arts Sci.*, **23**, 188 (1887).
[3] Hill and White, *Am. Chem. J.*, **27**, 193 (1902).
[4] Priebs, *Ber.*, **18**, 1362 (1885).
[5] Heuck, *Ber.*, **28**, 2256 (1895).
[6] Marquis, *Compt. rend.*, **132**, 140 (1901).
[7] Marquis, *Compt. rend.*, **134**, 776 (1902).
[8] Marquis, *Ann. chim.* (*8*), **4**, 196 (1905).
[9] Kimel, Coleman and Stillman (to Eaton Laboratories, Inc.), U. S. Pat. 2,490,006 (1949); *C. A.*, **44**, 1543 (1950).
[10] Witte and Lind (to Allied Chemical and Dye Corp.), U. S. Pat. 2,502,114 (1950).

pounds as antibacterial agents. This activity is particularly pronounced in 5-nitrofurfural semicarbazone, and related derivatives (p. 164).

Nitration of Furan and Its Homologs

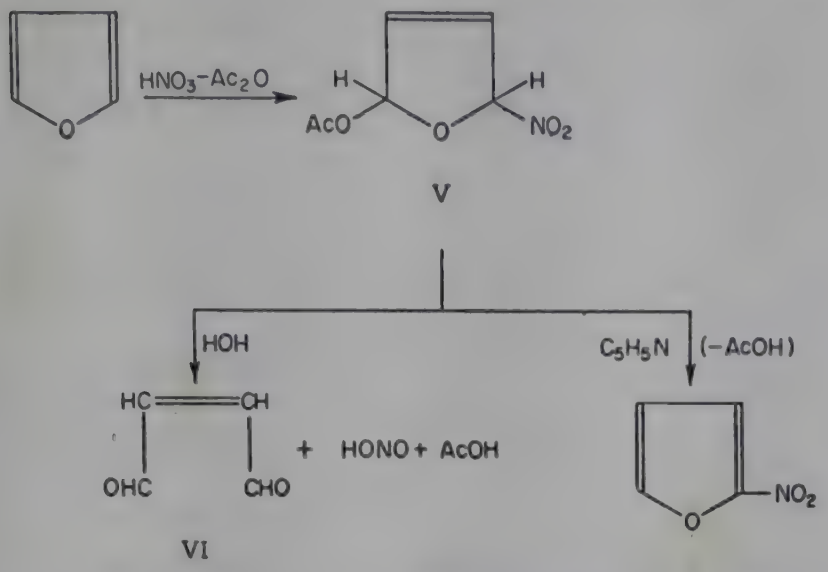
Successful nitration of furan is achieved only at low temperature, and under anhydrous conditions. The usual procedure makes use of acetic anhydride and fuming nitric acid, at approximately −10°. The acetic anhydride serves not only as a diluent and dehydrating agent, but also takes part in the reaction. In all probability the nitrating agent is the mixed anhydride of nitric and acetic acids. Thus, starting with furan, Marquis[7, 8] obtained an intermediate addition product (the so-called "nitroacetin") which analyzed correctly for $C_4H_4O \cdot AcONO_2$. A number of structures have been postulated for this intermediate. Marquis assigned the open-chain enol configuration (I), and concluded that the nitrofuran subsequently obtained by the action of pyridine was a β-substituted furan. This is, of course, at variance with the recognized preferential α-substitution in the furan series, and in the belief that the final product should have been 2-nitrofuran, Rinkes[11] proposed formula II for the adduct; Gilman and Burtner[12] suggested III, and Freure and Johnson[13] advocated IV or V. The available evidence is definitely in favor of formula V; that V is formed by a 1,4-type



addition to the furan nucleus. The adduct fails to absorb bromine from carbon tetrachloride solution[13] and of the structures indicated above, only V is reconcilable with this fact.[a] Furthermore, Clauson-Kaas and Fakstorp[14] have demonstrated conclusively that the addition product decomposes in water to form malealdehyde, VI (see also [7, 8]), and offer this result as decisive proof of configuration V. None of the other structures which have been postulated for the adduct would give malealdehyde on hydrolysis.

[a] Maleic anhydride does not absorb bromine from carbon tetrachloride solution. By analogy, a compound possessing structure V would be expected to behave in somewhat similar fashion.

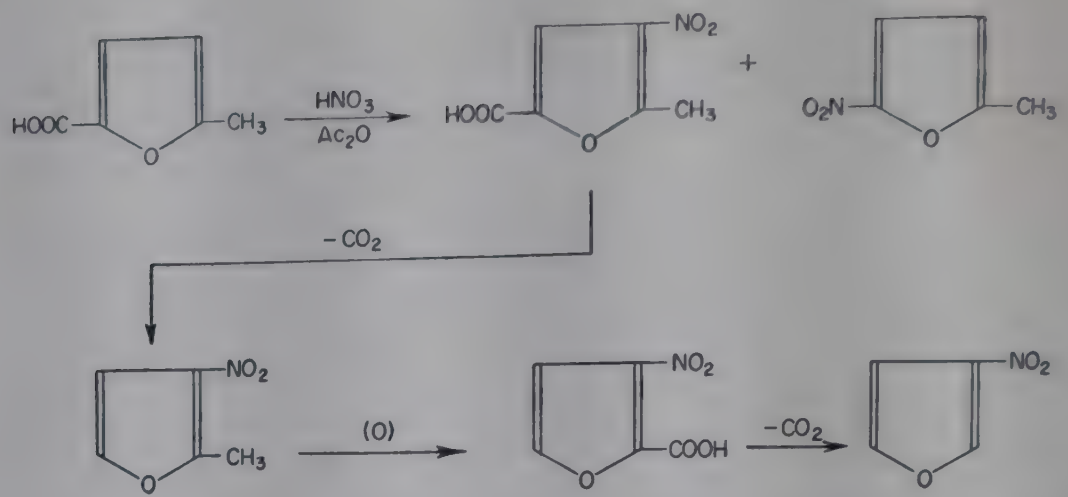
[11] Rinkes, *Rec. trav. chim.*, **49**, 1169 (1930).
[12] Gilman and Burtner, *Iowa State Coll. J. Sci.*, **5**, 189 (1931).
[13] Freure and Johnson, *J. Am. Chem. Soc.*, **53**, 1142 (1931).
[14] Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, **1**, 210 (1947).



As illustrated above, treatment of the intermediate addition compound with pyridine removes the elements of acetic acid with formation of a nitrofuran.[7, 8] Excluding rearrangement of the nitro group during this process, the product must be 2-nitrofuran and not the 3-isomer as originally[7, 8] supposed. In an attempt to establish this point, Freure and Johnson[13] showed Marquis' nitrofuran to be identical to that obtained on decarboxylation of the nitrofuroic acid formed subsequent to the nitration of methyl 2-furoate. Their proof of alpha-substitution rested on the identity of the nitrofuroic acid; assignment of the nitro group to the 5-position was based on the earlier work of Hill and White.[3] The latter investigators had obtained the same nitrofuroic acid by nitration of either 2,5-furandicarboxylic acid, or 5-sulfo-2-furoic acid, and had assumed that the incoming nitro group had replaced a carboxyl or a sulfonic acid group in the same position. Inasmuch as some nitrofuran was also found as a reaction product, however, it might still be argued that the nitro group substituted beta with concomitant decarboxylation.

A more rigid proof of the structure of the product obtained by direct nitration of furan may be derived from the work of Rinkes[11, 15, 16, 17, 18] who nitrated 5-methyl-2-furoic acid and obtained, in addition to a nitromethylfuran, a small amount of a mononitro compound with the methyl and carboxyl groups intact. In the latter compound, the nitro group must be attached to a β-nuclear carbon atom since both of the alpha positions are occupied. Rinkes decarboxylated this product, and obtained a β-nitro-2-methylfuran which he converted to β-nitro-2-furoic acid by oxidation with neutral potassium ferricyanide according to the method of Brown.[19] Decarboxylation of the latter gave β- or 3-nitrofuran, a product which was not identical to that obtained by Marquis.

[15] Rinkes, *Rec. trav. chim.*, **50**, 590 (1931).
[16] Rinkes, *Rec. trav. chim.*, **50**, 981 (1931).
[17] Rinkes, *Rec. trav. chim.*, **52**, 538 (1933).
[18] Rinkes, *Rec. trav. chim.*, **57**, 390 (1938).
[19] Brown, *Iowa State Coll. J. Sci.*, **11**, 227 (1937).



Since there can be but one alpha- and one beta-nitrofuran, Marquis' compound must be α- or 2-nitrofuran. It follows that the nitrofuroic acid obtained on nitration of 2-furoic acid has the nitro group attached to an alpha carbon atom (position 5) since 2-nitrofuran is obtained on decarboxylation.[13, 15]

The preparation of nitroalkylfurans by direct nitration is more difficult than with furan due to the increased sensitivity of the nucleus of alkylfurans to acidic reagents. However, 2-methylfuran, 3-methylfuran, and 2,5-di-

TABLE 1. NITRO DERIVATIVES OF FURAN AND ITS HOMOLOGS

Compound	Physical constants (°C.)	Ref.
Mononitro types		
2-Nitrofuran	m.p. 28, 28.8–29.2 b.p. 133–135 (123 mm.)	13, 20, 11, 15, 21, 8, 22
3-Nitrofuran	m.p. 27	18
2-Nitro-3-methylfuran	m.p. 32.6, 35 b.p. 105–106 (13 mm.)	20, 23
2-Nitro-4-methylfuran	m.p. 29	16
2-Nitro-5-methylfuran	m.p. 42.5–43.5, 45.5–46 b.p. 104 (12 mm.)	20, 24, 22; see also 25
2-Nitro-5-*t*-butylfuran	m.p. 68–70	22
2-Nitro-5-vinylfuran	m.p. 48–50	25a
2-Nitro-5-styrylfuran	m.p. 115	21
3-Nitro-2-methylfuran	m.p. 8, 9.4 b.p. 79 (10 mm.)	16, 18
3-Nitro-2-styrylfuran	m.p. 135	18
3-Nitro-2,5-dimethylfuran	b.p. 88–92 (9 mm.) d_{20}^{25} 1.52 n^{20} 1.3140	26
3-Nitro-2,5-dimesitylfuran	m.p. 107.5–108	27, 28
3-Nitro-2,5-bis(bromomesityl)furan	m.p. 130–130.5	28
3-Nitro-4-phenyl-2,5-dimesitylfuran	m.p. 164–165	29
3-Nitro-2,4,5-trimesitylfuran	m.p. 206.5–207	30

TABLE 1—*Continued*

Compound	Physical constants (°C.)	Ref.
Dinitro types		
2,5-Dinitrofuran	m.p. 100–101	31, 2, 3, 8; see also 25, 32
2,5-Dinitro-3-methylfuran	m.p. 88–90	16
3,5-Dinitro-2-methylfuran	m.p. 74	16
3,4-Dinitro-2,5-dimesitylfuran	m.p. 213	28
3,4-Dinitro-2-mesityl-5-(nitromesityl)furan	m.p. 158–160	28
3,4-Dinitro-2,5-bis(nitromesityl)furan	m.p. 266–267	28
3,4-Dinitro-2,5-bis(bromonitromesityl)furan	m.p. 245 (dec.)	28
3,4-Dinitro-2,5-bis(bromomesityl)furan	m.p. 200.5–201.5	28
5,5′-Dinitro-2,2′-bifuryl	m.p. 213–214	16

methylfuran have been nitrated successfully, albeit in low yield, by the previously described method of Marquis using acetic anhydride and fuming nitric acid at low temperature, followed by treatment of the intermediate addition product with pyridine.

Nitration of 2-methylfuran introduces a nitro group at the open alpha position to give 5-nitro-2-methylfuran, VII.[20] Rinkes' assignment of the nitro group to the open α-position was based on the fact that the same nitromethylfuran was formed as the major product following nitration of 5-methyl-2-furoic acid, and on the assumption that in this reaction the carboxyl group was replaced in the identical position.[b] A more unequivocal proof of the orientation is the fact that the nitromethylfuran in question

[b] Rinkes[17] argues for the general validity of this assumption as a means for determining orientation in the furan nucleus. The alternative, in the experiment cited, is preliminary formation of a β-nitro-5-methyl-2-furoic acid which then undergoes decarboxylation at the low temperature of nitration. Rinkes points out that this acid is actually obtained as a by-product, and that it fails to decarboxylate even at its melting point (160°).

[20] Rinkes, *Rec. trav. chim.*, **49**, 1118 (1930).

[21] Rinkes, *Rec. trav. chim.*, **51**, 349 (1932).

[22] Eaton Laboratories, private communication.

[23] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

[24] Gilman, Burtner and Smith, *Rec. trav. chim.*, **51**, 407 (1932).

[25] Nazarova and Syrkin, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1949**, 35; *C. A.*, **43**, 4913 (1949).

[25a] Wiley and Smith, *J. Am. Chem. Soc.*, **72**, 5198 (1950).

[26] Gilman and Burtner, *Rec. trav. chim.*, **51**, 667 (1932).

[27] Lutz, Johnson and Wood, *J. Am. Chem. Soc.*, **60**, 716 (1938).

[28] Lutz and Kibler, *J. Am. Chem. Soc.*, **62**, 1520 (1940).

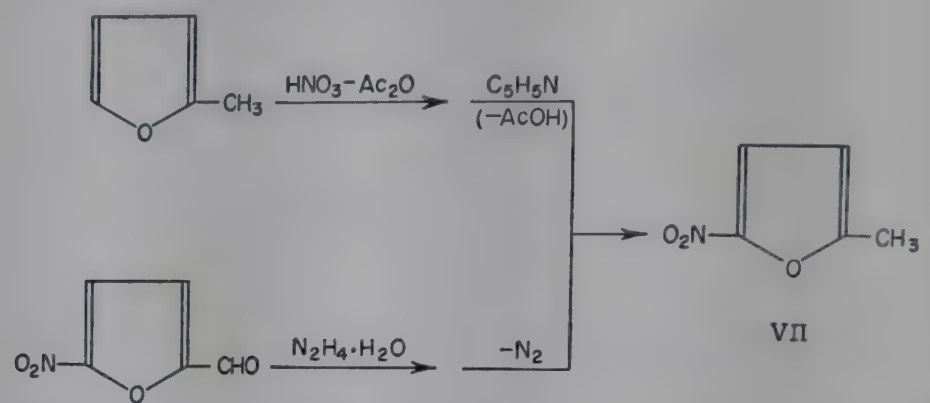
[29] Lutz and Kibler, *J. Am. Chem. Soc.*, **61**, 3010 (1939).

[30] Lutz and Kibler, *J. Am. Chem. Soc.*, **62**, 360 (1940).

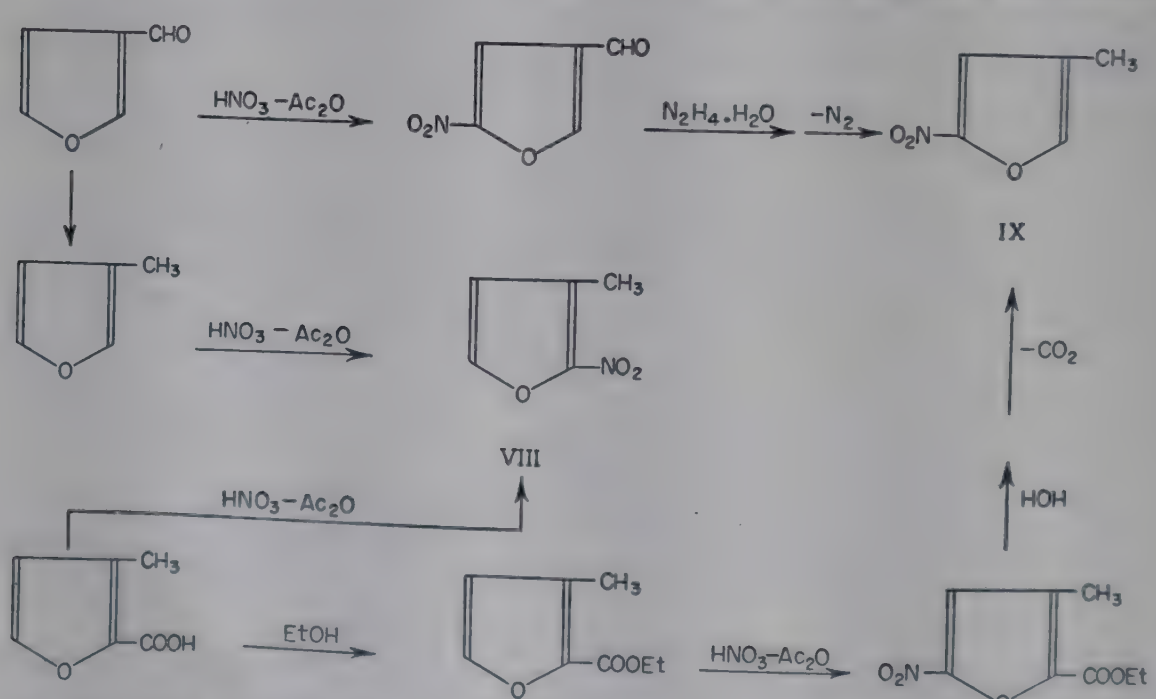
[31] Hill and Palmer, *Am. Chem. J.*, **10**, 373 (1888).

[32] Gilman, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **6**, 137 (1932).

was also obtained by a Wolff-Kizhner reduction of 5-nitrofurfural[33] (see also p. 155). The location of the nitro-substituent of the latter compound is known; on oxidation it is converted into what has been shown to be 5-nitro-2-furoic acid (see page 157).



The remaining two α-nitro-methylfuran isomers, 2-nitro-3-methylfuran, VIII[23, 20] and 2-nitro-4-methylfuran, IX[23, 16] are also known. Each was synthesized by two different methods, and the structures are established with reasonable certainty. The methyl group in each must be attached to a β-nuclear carbon atom by virtue of the starting materials (see diagram below). Assignment of the nitro group to an alpha carbon is on the basis of the general tendency for substituting groups to orient to an alpha position if such a location is available, or if an easily replaceable group is so situated.



The reactions depicted above have an important bearing on the subject of nuclear substitution and orientation of furan types. They indicate the

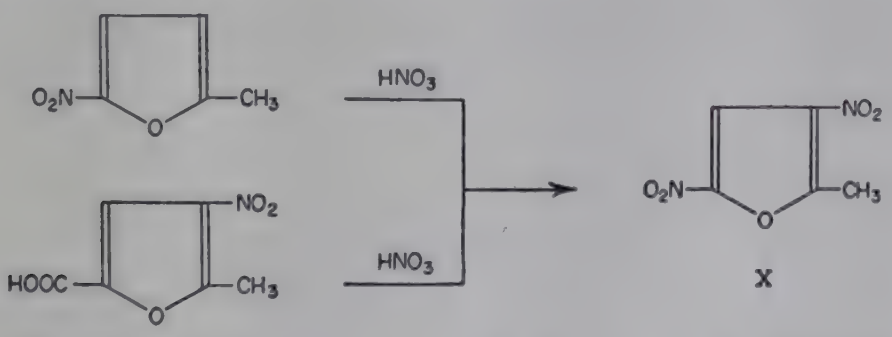
[33] Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).

directing influence of β-methyl and β-formyl groups on an entering nitro radical when both alpha positions are unoccupied. The β-formyl group orients to the more remote α-position, whereas nitration of 3-methylfuran introduces a nitro group at the adjacent α- or 2-position. In the latter instance, the product yield reported[23] is distressingly low and the possibility may not be excluded that some of the isomeric 2-nitro-4-methylfuran was also formed, although it was not isolated.

Only one of the three isomeric β-nitromethylfurans has been described. It was obtained by indirect means; nitration of 5-methyl-2-furoic acid and decarboxylation of the resulting β-nitro-5-methyl-2-furoic acid.[20, 16] Rinkes[16, 17] assigned the nitro group of the acid to the 4-position, and therefore the structure of 3-nitro-2-methylfuran to the product of decarboxylation. The homologous 3-nitro-2,5-dimethylfuran was obtained by nitration of 2,5-dimethylfuran, and also by decarboxylation of 2,5-dimethyl-4-nitro-3-furoic acid.[26, 34]

The stabilizing effect of the nitro group on the nucleus of mononitrofurans permits further nitration with no special precautions. Marquis[35, 8] treated his mononitrofuran with nitric acid directly to obtain a dinitro derivative which he showed to be identical with that described earlier by Hill[31, 3] as 2,5-dinitrofuran (see p. 157). No tri- or tetranitrofuran has been reported. It is unlikely that such products could be prepared by direct nitration in view of the general deactivation of the nucleus by negative substituents.

5-Nitro-2-methylfuran on further nitration with a mixture of nitric and sulfuric acids at −10°, gives a product to which Rinkes[16] has assigned the structure of 3,5-dinitro-2-methylfuran, X. The same product has also been obtained by nitration of 5-methyl-4-nitro-2-furoic acid.[16] It must be admitted, however, that the evidence for the assignment of the beta-nitro group to the position indicated is not conclusive. By the action of nitric

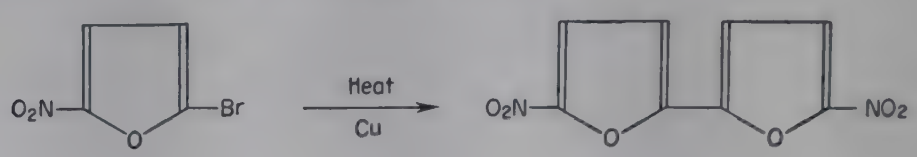


acid on 2-nitro-3-methylfuran, a second nitro group is introduced; most probably at the open alpha-position to give 2,5-dinitro-3-methylfuran.[16]

[34] Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932).
[35] Marquis, *Compt. rend.*, **135**, 505 (1902).

As a result of his studies, Rinkes[21] formulated general rules of orientation. Thus, nitration in the furan series leads, if at all possible, to α-substitution. In some instances, this may involve removal of such resident groups as carboxyl, sulfo and acetyl. If both alpha positions are occupied by irreplaceable substituents, β-substitution may occur.

In his work on the nitration of furan, Marquis[8] reported the formation of a small quantity of an unidentified by-product, the analysis of which corresponded to the composition $C_8H_4O_6N_2$. Rinkes[16] showed this product to be 5,5′-dinitro-2,2′-bifuryl, XI, which he synthesized by coupling 5-bromo-2-nitrofuran using activated copper at 200°.

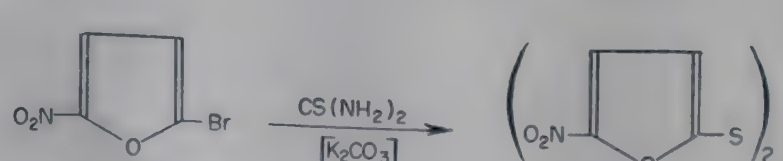


XI

Several arylfurans have been nitrated successfully using a mixture of nitric and acetic acids. Thus 2,3,5-trimesitylfuran produces a mononitro derivative in which the nitro group has been assigned to the open beta position of the furan ring.[30] Similarly 2,5-dimesitylfuran was nitrated in two steps to obtain first 2,5-dimesityl-3-nitrofuran, and then, on further nitration, the 3,4-dinitro product.[27, 28] A mononitro derivative was obtained from 2,5-bis(bromomesityl)furan, but there was surprising resistance to the introduction of a second nitro group.[28] In these instances, allocation of the nitro substituent to the furan nucleus rather than to the mesityl nuclei is based on indirect evidence, which though not conclusive, is reasonable.

Nitrohalofurans:

5-Bromo-2-nitrofuran, b.p. 118° (15 mm.); m.p. 48°. Formed by action of HNO_3-Ac_2O on 5-bromo-2-furoic acid.[16] When placed in reaction with thiourea in the presence of potassium carbonate, it gives rise to 5,5′-dinitro-2,2′-difuryldisulfide, m.p. 97–99°, which was found to be very active in inhibiting the growth of strains of staphylococcus *in vitro*.[36]



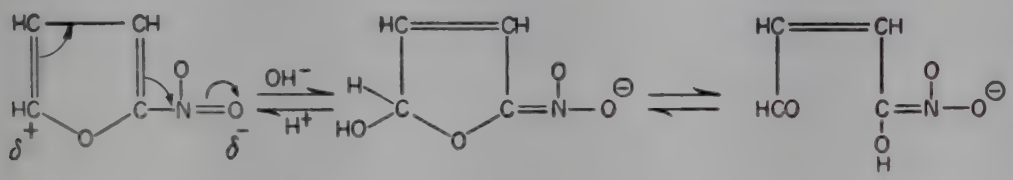
5-Iodo-2-nitrofuran, m.p. 76°. Prepared by treatment of 5-nitro-2-furylmercuric chloride with aqueous I_2-NaI.[37] Also formed, in low yield, by reacting 2,5-diiodofuran with HNO_3-Ac_2O reagent.[37] Compound is a strong lachrymator, sternutator and vesicant.

[36] Dann and Möller, *Chem. Ber.*, **80**, 21 (1947).
[37] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

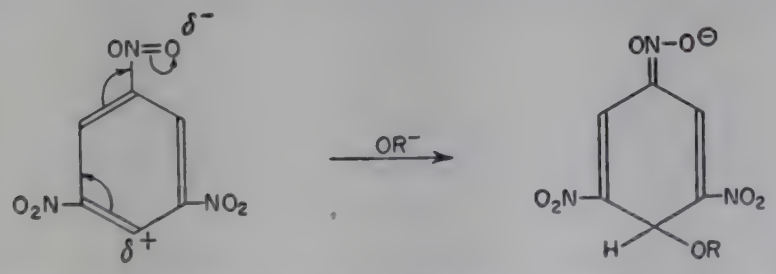
3,4-Dibromo-2,5-dinitrofuran, m.p. 150–151°. Obtained as by-product in the reaction of 3,4-dibromo-5-sulfo-2-furoic acid with fuming nitric acid.[2]

In contrast to the furans themselves, the nitrofurans are notably stable toward acidic reagents as witnessed by the fact that many compounds of this type can be further nitrated directly with fuming nitric acid or mixtures of nitric and sulfuric acids. Additional examples of this stability appear in the later sections of this chapter, but it seems worthwhile to mention at this point an outstanding illustration of the deactivating effect of the nitro group on the furan nucleus, namely, the formation of 5-nitro-2-furoic acid by oxidation of 5-nitro-2-furfural diacetate with *aqua regia*.[38]

The stabilizing influence of the nitro substituent, however, is observed only in neutral or acidic media. The α-nitrofurans are readily attacked by alkalies, in which they decompose to give nitrites and products possessing aldehyde characteristics.[8, 3] Thus, 2-nitrofuran resinifies in aqueous sodium hydroxide. This behavior possibly involves nuclear attack by hydroxyl ion, and subsequent readjustment of bonds (see Chapter 14):



A related explanation has been proposed to account for the colored salts formed by the addition of potassium methoxide to polynitro derivatives of benzene. For purposes of comparison, the postulated structure for one of these salts[39] is also shown in the diagram which follows. In the case of the nitrofuran, however, the configuration of the salt is that of an unsaturated cyclic hemiacetal, which would explain the instability and ready resinifica-



tion observed. Accordingly, strong alkali must be avoided in working with the nitrofurans. Weak bases, such as sodium bicarbonate, pyridine, quinoline and other tertiary amines may be used where necessary.

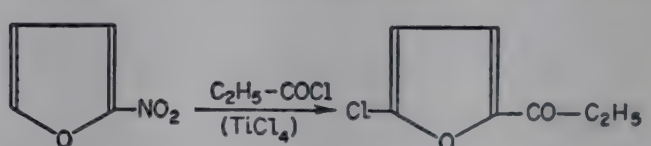
Deactivation of the furan nucleus toward acidic reagents is further evidenced by the failure of attempted bromination of 2-nitrofuran. The latter

[38] Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 2550 (1930).

[39] Karrer, "Organic Chemistry," p. 382, New York, Nordemann Publishing Company (1938).

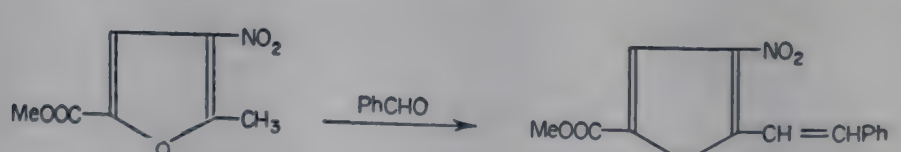
is recovered unchanged in large measure, under conditions which promote ready substitution of other furan derivatives.[40] Similarly, the presence of the nitro group in 2,5-dimesityl-3-nitrofuran prevents substitution of bromine for hydrogen on the remaining furan beta-carbon atom; the bromine enters the mesityl nucleus.[28] In both of the above reactions, further nitration is possible if fuming nitric acid is used; but bromination is inhibited by the nitro group already present. Apparently the strongly acidic medium, and the elevated temperature employed in the nitration exert a labilizing action sufficient to overcome the deactivating influence of the nitro substituent.

Attempts to acylate and alkylate nitrofurans under a variety of conditions, and with different condensing agents have also been futile.[41, 42] In this regard, Gilman, *et al.*[43] report a peculiar occurrence in attempting a comparison of 2-nitrofuran with nitrobenzene on the basis of ease of acylation by the Friedel-Crafts reaction. They employed titanium chloride as the catalyst in condensing the nitrofuran with propionyl chloride in carbon disulfide, and quite unexpectedly obtained 5-chloro-2-furyl ethyl ketone, XII. The mechanism of this reaction was not studied, and the object of the experiment was nullified, due to the displacement of the nitro group.

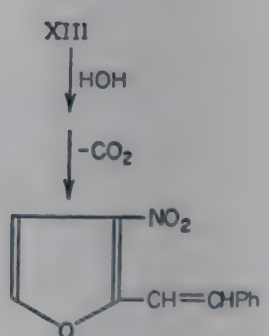


XII

In the presence of a trace of piperidine at 120°, 2-methyl-5-nitrofuran condenses with benzaldehyde to give 2-styryl-5-nitrofuran in low yield. Methyl 5-methyl-4-nitro-2-furoate condenses much more readily under the same conditions. The resulting ester, XIII, on hydrolysis and decarboxylation, gives rise to 2-styryl-3-nitrofuran, XIV.[21, 18] Thus, the nitro group



XIII



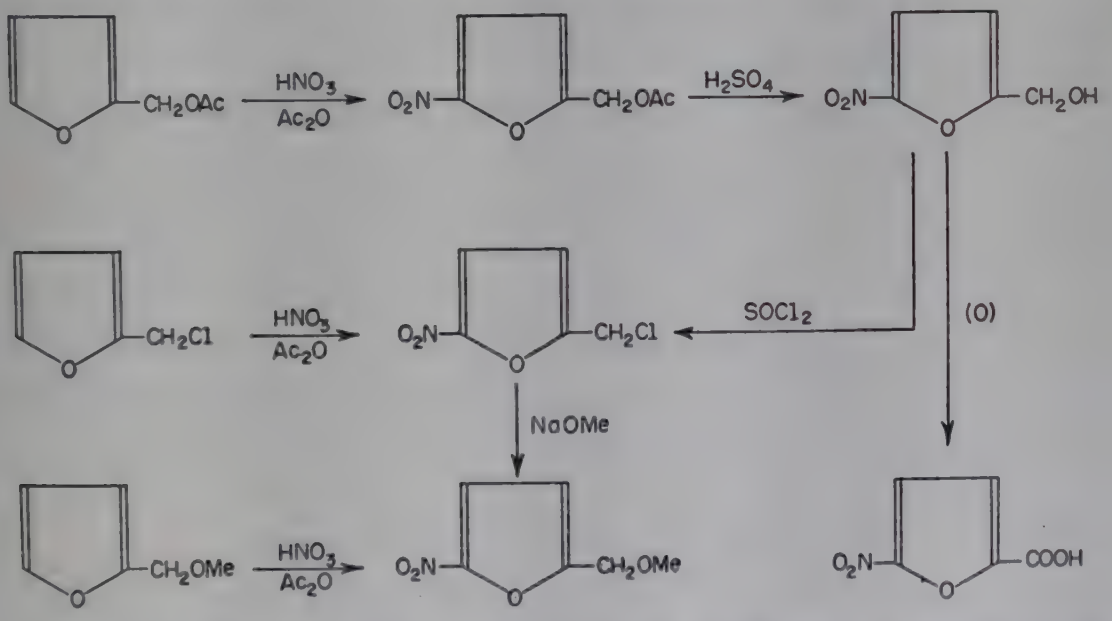
XIV

has the expected labilizing effect on the hydrogen atoms of the methyl substituent. The effect seems to be even more pronounced than is shown by related compounds in the benzene series. For example, *o*- and *p*-nitrotoluene failed to react with benzaldehyde under the conditions employed with the furan analogs.[21]

Marquis[8] attempted reduction of the simple nitrofurans with various reducing agents (aluminum amalgam, zinc and acetic acid, etc.), but failed to obtain the desired furylamines. In several instances, he obtained unidentified products possessing aldehyde characteristics, indicating that the nucleus had been ruptured. As would be expected, he had more success in reducing nitrofuroic esters, because of the stabilizing effect of the carbalkoxy substituent (see p. 188). For the insecticidal properties of 2-nitrofuran, see Yeager *et al.*[44]

Nitrofurfuryl Alcohol and Its Derivatives

Gilman and his students successfully applied the Marquis nitration technique to 2-furfuryl esters and ethers.[45, 46] As before, an oily, intermediate, addition product is first formed, and this is converted into the appropriate nitrofuran by the action of pyridine. The point of attachment of the nitro



group is evidently the same in all cases as shown by the interconversion of these products. Its assignment to the 5-position is based on the forma-

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[40] Gilman and Wright, *Chem. Revs.*, **11**, 323 (1932).
[41] Calloway, *Iowa State Coll. J. Sci.*, **9**, 141 (1934).
[42] Calloway, *Chem. Revs.*, **17**, 327 (1935).
[43] Gilman, Burtner, Calloway and Turck, *J. Am. Chem. Soc.*, **57**, 907 (1935).
[44] Yeager, Woolley and Brown, *Proc. Soc. Exptl. Biol. Med.*, **30**, 19 (1932).
[45] Gilman and Wright, *J. Am. Chem. Soc.*, **53**, 1923 (1931).
[46] Gilman and Burtner, *Iowa State Coll. J. Sci.*, **6**, 389 (1932).

tion of 5-nitro-2-furoic acid and 5-nitrofurfural when the nitrofurfuryl alcohol is oxidized with manganese dioxide in sulfuric acid.[45, 46] From the corresponding chloride, Takahashi *et al.*[47] prepared several 5-nitrofurfuryl sulfides (thioethers) in order to study their antibacterial activity. The activity of 5-nitrofurfuryl propionate toward *Staphylococcus aureus* was studied by Cramer and Dodd.[48]

TABLE 2. 5-NITROFURFURYL ALCOHOL AND ITS DERIVATIVES

5-Nitrofurfuryl	Physical constants (°C.)	Ref.
Alcohol	m.p. 32	45
Acetate	m.p. 47	45
Propionate	—	9, 48
Chloride*	b.p. 122–124 (6 mm.) d_{20}^{20} 1.429 n_D^{20} 1.5688	46; see also 47
Methyl ether	b.p. 114–117 (4 mm.) d_{20}^{20} 1.283 n_D^{20} 1.5343	46
Sulfide	m.p. 98–99	47
Phenyl sulfide	b.p. 158–163 (10 mm.)	47
p-Nitrophenyl sulfide	m.p. 113–114	47
5-Nitro-2-pyridyl sulfide	m.p. 145–146	47

* Care should be exercised in working with this compound because of its vesicant action; approximately $\frac{1}{150}$ that of mustard gas.[46, 32]

The stabilizing effect of the nuclear nitro group in these compounds is apparent by comparison of their resistance to acidic reagents with that of their generators. Most striking, perhaps, is the behavior of 5-nitro-2-furfuryl methyl ether on treatment with hydriodic acid. Whereas 2-furfuryl methyl ether is relatively unstable and resinifies readily, the nitrofurfuryl ether is largely recovered unchanged under the general conditions for splitting ethers.[46] In other words, the nitro group not only deactivates the nucleus toward acidic reagents, but also imparts to the lateral ether group a high degree of resistance to cleavage.

NITRATED ALDEHYDES AND KETONES

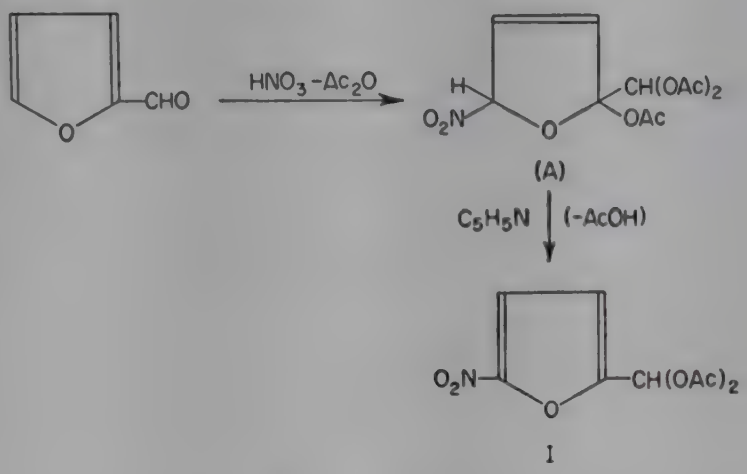
As early as 1902, Marquis[35] attempted the nitration of furfural, but it was many years later before Gilman and Wright[38, 49] described the first nitrofurfural. Using fuming nitric acid in acetic anhydride, they were able to obtain 5-nitrofurfural diacetate, I, starting with either furfural itself or furfural diacetate. The intermediate addition compound, A, was isolated as a crystalline product melting at 106–107°, which could be converted quantitatively into the nitro substitution product by solution in pyridine

[47] Takahashi, Saikachi, Sasaki and Kimura, *J. Pharm. Soc. Japan*, **69**, 289 (1949); *C. A.*, **44**, 5373 (1950).

[48] Cramer and Dodd, *J. Bact.*, **51**, 293 (1946).

[49] Gilman and Wright, *J. Am. Chem. Soc.*, **52**, 4165 (1930).

and precipitation by dilution with water. Other weak bases, such as dimethylaniline, were found to be satisfactory for effecting the elimination of acetic acid from the intermediate. Hydrolysis of the diacetate gave the nitro aldehyde, the position of the nitro group being established by oxidation to 5-nitro-2-furoic acid.



I

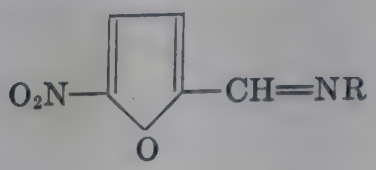
The isomeric 5-nitro-3-furaldehyde was synthesized in like manner from 3-furaldehyde or the corresponding diacetate.[23, 50]

Attempts to introduce a second nitro group into I by a variety of methods resulted in failure.[51] In addition to the customary procedure, mixtures of nitric and sulfuric acids were employed, even at elevated temperature, as well as the method of Menke,[52] using cupric nitrate in acetic anhydride at

TABLE 3. NITROFURAN ALDEHYDES AND KETONES

Compound (m.p., °C.)	Derivatives (m.p., °C.)		Ref.
Aldehydes			
5-Nitrofurfural (35–36)	diacetate	92.5	38, 45
	oxime	121, 153	
5-Nitro-3-furaldehyde (76)	diacetate	87	23, 50
	semicarbazone	215 (dec.)	
3-(5-Nitro-2-furyl)acrolein (117–118)	semicarbazone	238–240	53; see also 53a
	thiosemicarbazone	dec. < 250	
5-Nitro-2-furyl ketones			
Methyl (78.5)	oxime	167–168	21, 54
	semicarbazone	250	
Diazomethyl (113–114.5)	—		55
Hydroxymethyl (116–117.5)	semicarbazone	197–200 (dec.)	55
Phenyl (111)	—		56
p-Tolyl (122–123)	—		57
p-Methoxyphenyl (126–127)	—		57
4-Methoxy-3-nitrophenyl (123–124)	—		57
2-Thienyl (161)	—		56

TABLE 4. SOME NITROGEN DERIVATIVES OF 5-NITROFURFURAL



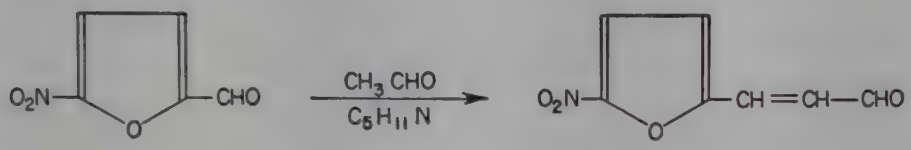
R	M.p. (°C.)	Ref.
Aldimines		
p-C_6H_4OH	179 (dec.)	53
p-$C_6H_4OCH_3$	130	53
p-C_6H_4Cl	158	53
p-$C_6H_4NO_2$	170	53
p-C_6H_4COOH	227 (dec.)	53
p-C_6H_4(*p*-$SC_6H_4NO_2$)	168 (dec.)	53
1-$C_{10}H_7$	99–101	53
2-$C_{10}H_7$	155–156	53
3-C_5H_4N	118–120 (dec.)	53
Hydrazones		
—NHC_6H_4Br-*p*	201 (dec.)	53
—$NHCOCH_3$	230–235 (dec.)	58
—$NHCOCH_2NH_2$	206–208 (dec.)(**HCl salt**)	58
Semicarbazones and related types		
—$NHCONH_2$ (Furacin)	liquifies in the range 227–241	58, 48; see also 58a
—$NHCSNH_2$	black at 250	58; see also 58a
—$NHCONHCH_3$	201–202	58
—$N(CH_2CH_2OH)CONH_2$ (Furadroxyl)	214–216 (dec.)	58
—$NHCONHCONH_2$	210.5–211.5 (dec.)	58
—$NHCONHC(NH)NH_2$	221–225 (dec.)(**HCl salt**)	58
Semioxamazones		
—$NHCOCONH_2$	250, 260 (dec.)	58, 53
—$NHCOCONHCH_2CH_2OH$	242–244 (dec.)	58

[50] Hayes, *J. Am. Chem. Soc.*, **71**, 2581 (1949).
[51] Gilman and Young, *Rec. trav. chim.*, **51**, 761 (1932).
[52] Menke, *Rec. trav. chim.*, **44**, 141 (1925).
[53] Takahashi, Saikachi, Yoshina and Mizuno, *J. Pharm. Soc. Japan*, **69**, 284 (1949); *C. A.*, **44**, 5372 (1950).
[53a] Saikachi *et al.*, *Japan J. Pharm. & Chem.*, **22**, 258 (1950); *C. A.*, **45**, 4887 (1951).
[54] Brown, *Iowa State Coll. J. Sci.*, **11**, 221 (1937).
[55] Stillman and Scott (to Eaton Laboratories, Inc.), U. S. Pat. 2,416,235 (1947); *C. A.*, **41**, 3488 (1947).
[56] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 464 (1934).
[57] Straley, *Iowa State Coll. J. Sci.*, **11**, 115 (1936).
[58] Stillman and Scott (to Eaton Laboratories, Inc.), U. S. Pats. 2,416,233–4, 2,416,236–9 (1947); *C. A.*, **41**, 3488–9 (1947).
[58a] Hoggarth, Taubman and Imperial Chemical Industries Ltd., Brit. Pat. 620,888 (1949); *C. A.*, **44**, 5548 (1950).

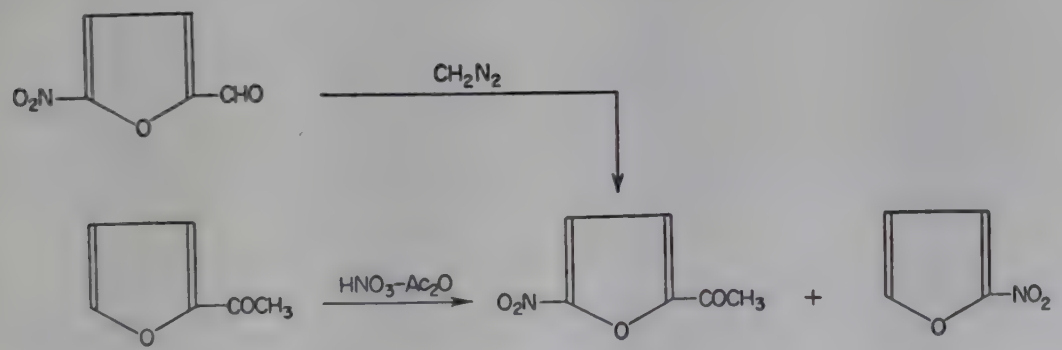
50° for 72 hours. The nitrofurfural diacetate was recovered in varying amounts up to complete recovery, still another indication of the stability of the nitrofurans toward acidic reagents.

As mentioned previously, 5-nitrofurfural and the isomeric 5-nitro-3-furaldehyde have been reduced to the corresponding nitromethylfurans.[33, 23] This was accomplished by a modification of the Wolff-Kizhner technique; the sensitivity of nitrofuran types to strong bases precludes the use of caustic soda or sodium ethoxide for the final step of the synthesis involving the elimination of nitrogen from the hydrazone derivative of the nitro aldehyde. Success was achieved, however, by heating the hydrazone with copper-bronze in quinoline.

With acetaldehyde in the presence of a small amount of piperidine, 5-nitrofurfural condenses to form 3-(5-nitro-2-furyl)acrolein, although the reported yield (< 30 per cent) leaves something to be desired[53] (see also [53a]).

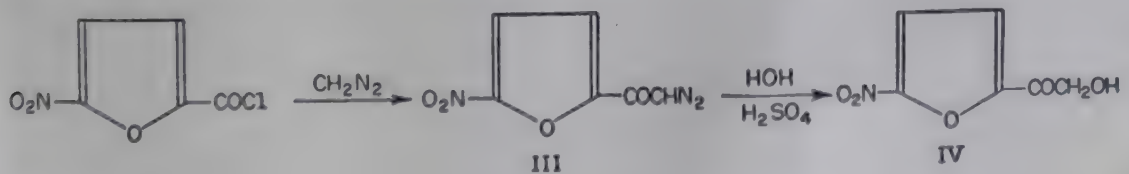


The action of diazomethane on 5-nitrofurfural gives rise to 5-nitro-2-furyl methyl ketone, II,[54] which is also the major product obtained by nitration of 2-furyl methyl ketone.[21] In the latter reaction, partial replacement of the acetyl group occurs as evidenced by the isolation of 2-nitrofuran as a by-product.



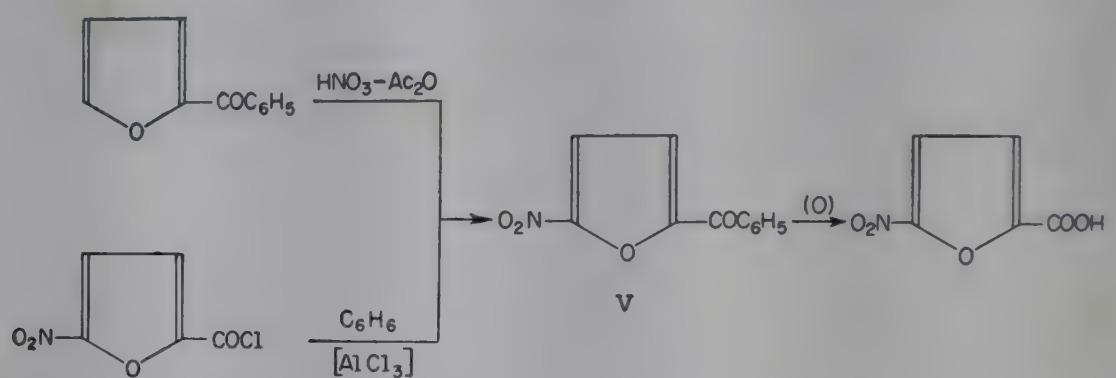
II

5-Nitro-2-furyl hydroxymethyl ketone, IV, was synthesized by way of the diazomethyl ketone, III, obtained by reacting diazomethane with 5-nitro-2-furoyl chloride.[55] For the therapeutic activity of the semicarbazone derivatives of I, II and IV, see Table 9.

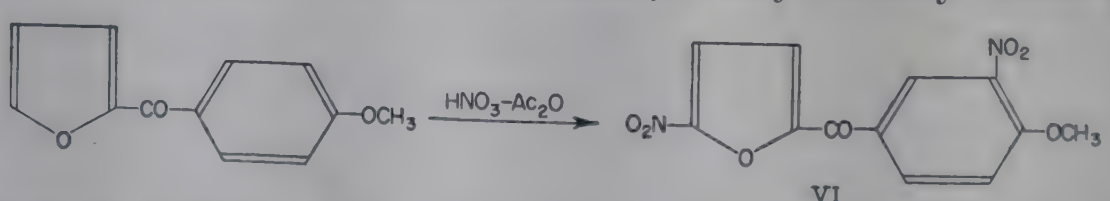


III IV

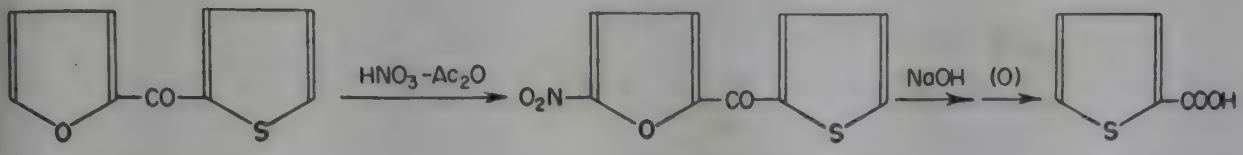
The nitration of several furyl aryl ketones was carried out by Gilman and his students in connection with studies of the relative ease of substitution of the furan nucleus as compared with other aromatic types. Thus, furyl phenyl ketone yielded 5-nitro-2-furyl phenyl ketone, V, on treatment with fuming nitric acid in acetic anhydride.[56] Proof of the location of the nitro group was established in two different ways. First, the same nitro ketone was synthesized by the Friedel-Crafts reaction from 5-nitro-2-furoyl chloride and benzene; second, permanganic acid oxidation of the nitro ketone resulted in the formation of 5-nitro-2-furoic acid and a small amount of benzoic acid.[56] Nitration of the related 2-furyl *p*-tolyl ketone likewise



gave a mononitro ketone[57] in which it is reasonable to suppose the nitro group is attached to the 5-position of the furan nucleus. When the benzene ring possesses an alkoxy substituent, however, both nuclei are nitrated. Thus Straley[57] described 5-nitro-2-furyl 4-methoxy-3-nitrophenyl ketone, VI, as the product of nitration of furyl *p*-methoxyphenyl ketone, even when precautions were taken to effect mono-nitration. Therefore, it would appear that the more facile replacement of a hydrogen atom in the furan nucleus as compared to the benzene ring is due to the activating influence of the heterocyclic oxygen. Similarly, 2-furyl 2-thienyl ketone was



nitrated to determine the comparative ease of nitration of the furan and thiophene nuclei. The mononitro ketone (VII) so obtained was found to be quite resistant to oxidation in an acidic medium, and attempted synthesis by the alternative Friedel-Crafts procedure failed. That the nitro group was attached to the furan nucleus was ascertained indirectly. After treatment of the nitro ketone with strong alkali to destroy the nitrated nucleus, oxidation with permanganate gave 2-thenoic acid.

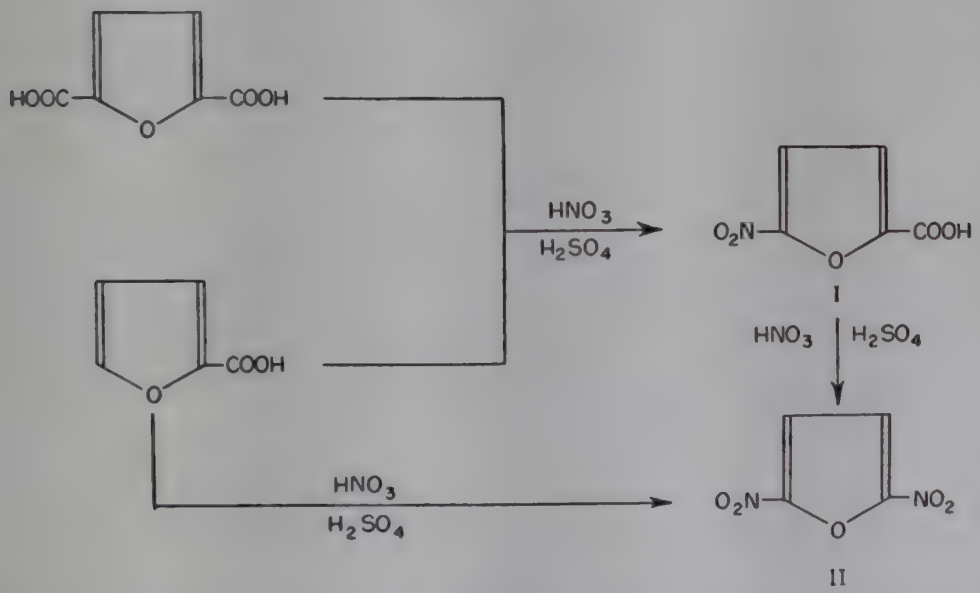


VII

Nitrated Furan Acids

Nitrofuroic Acids

Many furancarboxylic acids are sufficiently stable to permit direct nitration with fuming nitric acid or mixtures of nitric and sulfuric acids. Frequently, however, the carboxyl group is removed in the course of reaction, especially if it is situated alpha in the ring, so that nitrofurans as well as nitrofuroic acids are obtained. Thus, Hill and White[3] isolated 5-nitro-2-furoic acid, I, and a dinitrofuran as products of the action of a mixture of nitric acid and sulfuric acid on 2-furoic acid. Earlier, Klinkhardt[1] had obtained the same nitrofuroic acid by replacement of one of the carboxyl groups of 2,5-furandicarboxylic acid using the same reagent. The dinitrofuran was also obtained from 5-nitro-2-furoic acid under these conditions,[3] and is most probably 2,5-dinitrofuran, II, based on the mode of formation

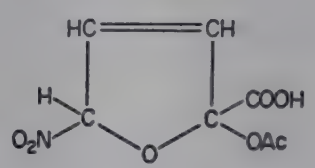


II

As might be supposed, in view of these results, sulfonic acid groups may likewise be replaced by a nitro group. For example, Hill and Palmer[2, 59] obtained I by treating 5-sulfo-2-furoic acid with concentrated nitric acid at ordinary temperatures or, more rapidly, at 100°. Later it was found that the reaction proceeds in two directions simultaneously, and that 5-nitro-2-furansulfonic acid is also formed.[3] The latter, like 5-nitro-2-furoic acid, is converted into 2,5-dinitrofuran by the continued action of nitric acid.[3]

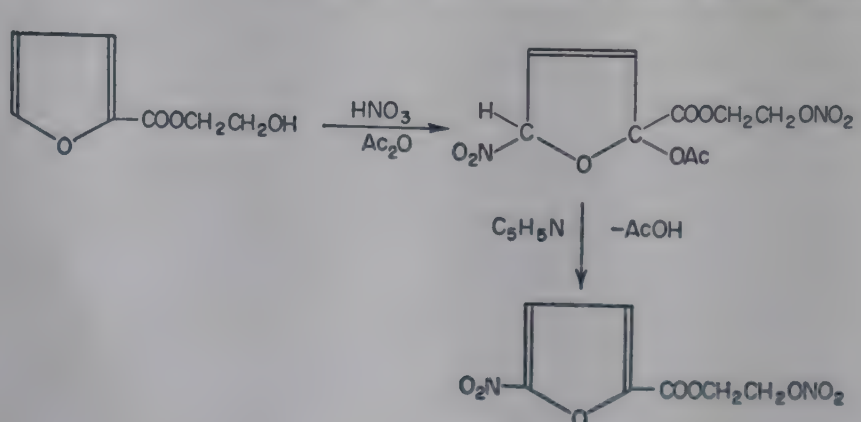
[59] Hill and Palmer, *Am. Chem. J.*, **10**, 409 (1888).

As indicated previously (p. 143), decarboxylation may also occur when nitration is effected using a mixture of nitric acid and acetic anhydride as the reagent. Actually, the extent to which this takes place is dependent upon the experimental conditions. Gilman and Burtner[26] have shown that rapid addition of the starting furancarboxylic acid to the nitrating mixture results in a very vigorous reaction leading to extensive decarboxylation, whereas slow addition permits closer control of the reaction temperature and a higher yield of the nitro acid. Protection of the carboxyl group by esterification is also helpful in minimizing its removal during nitration. In this regard, Freure and Johnson[13] make the interesting observation that, whereas 2-furoic esters form intermediate addition products on treatment with fuming nitric acid in acetic anhydride, no such product can be isolated on similar nitration of the free acid. They suggest that the mechanism is essentially the same in both reactions, the difference being due to the greater lability of the intermediate from the free acid. Assuming structure A for this intermediate, facile decarboxylation is understandable since A is a vinylog of a β-nitro carboxylic acid.



(A)

The nitration of hydroxyalkyl 2-furoates proceeds smoothly with the nitric acid and acetic anhydride reagent. Thus, 2-hydroxyethyl 2-furoate is converted into a crystalline intermediate (m.p. 124–125°; crystallizes with one molecule of methanol) which, after treatment with pyridine, gives rise to 2-nitratoethyl 5-nitro-2-furoate, III. Several *exo*-nitro-5-nitrofurans of this type were synthesized in order to evaluate them as explosives.[60]



III

[60] Gilman and Yale, *J. Am. Chem. Soc.*, **72**, 3593 (1950).

TABLE 5. NITROFUROIC ACIDS AND SOME DERIVATIVES

Compound (m.p.,°C.)	Derivatives (m.p.,°C.)	Ref.
2-Furoic acids		
5-Nitro (185–185.5)	esters:	13, 38, 46, 61,
	methyl (81.6)	56, 60, 11, 57,
	ethyl (99–100, 101)	62, 1, 4, 2, 8,
	2-nitratoethyl (81–82) (MeOH)	25
	2-nitratopropyl (70–71)	
	3-chloro-2-nitratopropyl (73–74)	
	phenyl (121–121.5)	
	acid chloride (38; b.p. 110–123 (4 mm.))	
	nitrile (67.8)	
3-Nitro (125)	—	18
3-Methyl-5-nitro (160)	ethyl ester (61)	16
5-Methyl-4-nitro (159–160)	methyl ester (81)	20, 21
5-Styryl-4-nitro (237)	methyl ester (151)	18, 21
5-Amino-4-nitro (—)	ethyl ester (150)	21
5-Acetamido-4-nitro (—)	ethyl ester (138)	21, 63
3-Furoic acids		
5-Nitro (138)	ethyl ester (56)	23
2-Methyl-5-nitro (154–154.5)	ethyl ester (52.5)	24, 61, 12
4-Methyl-5-nitro (194)	ethyl ester (42)	63a
2,4-Dimethyl-5-nitro (182)	—	26, 61
2,5-Dimethyl-4-nitro (176)	ethyl ester, b.p. 119-120 (20 mm.)	26

Rather interesting results were reported by Straley[57] with reference to the nitration of several aryl furoates, although the experimental details were not described. Phenyl 2-furoate gave rise to the corresponding 5-nitro-2-furoic ester, IV, indicating that alpha nitration of the 2-furoyl radical occurs more readily than nitration of a phenoxy group. On the other hand, the relative reactivity of the two nuclei is altered by introduction of a methoxy group into the benzene ring. For example, mono-nitration of *m*-methoxyphenyl 2-furoate gives a mixture of 3-methoxy-6-nitrophenol and its furoic ester, V. Starting with phenyl 2,5-furandicarboxylate, Straley obtained picric acid, showing that unsubstituted phenoxy groups are more susceptible to nitration than is the furan ring when both alpha positions are occupied by electronegative groups. These reactions are depicted below. For convenience the products are, in each case, shown in the form of the appropriate ester.

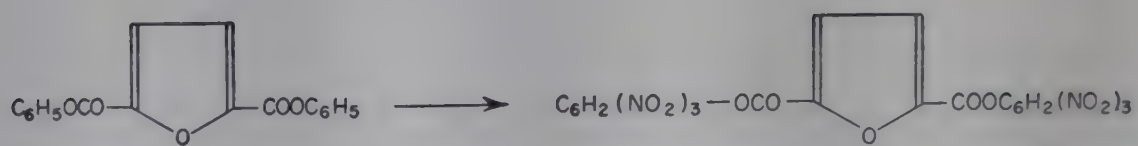
[61] Gilman, Janney and Bradley, *Iowa State Coll. J. Sci.*, **7**, 429 (1933).
[62] Dann, *Ber.*, **76**, 419 (1943).
[63] Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931).
[63a] Gilman and Burtner, *J. Am. Chem. Soc.*, **71**, 1213 (1949).



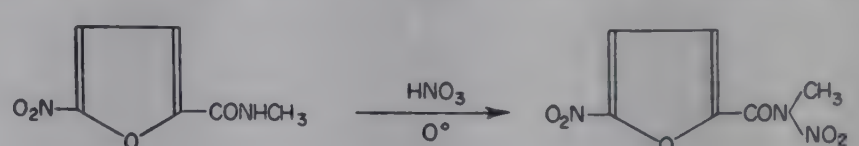
IV



V

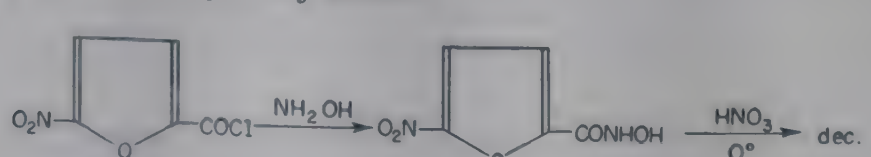


In common with other nitrofurans, the nitrofuroic acids are sensitive to alkalies, but stable in acidic medium. Accordingly, hydrolysis of the esters is best accomplished by heating with aqueous acid. With phosphorus pentachloride the nitro acid is converted into the acyl chloride from which amido derivatives may be synthesized by the action of ammonia or amines.[8, 60] When N-methyl-5-nitrofuramide, VI, was placed in reaction with fuming nitric acid at 0°, N-methyl-N,5-dinitrofuramide, VII (m.p. 89–90°) was obtained in 65 per cent yield.[60] Quite surprisingly, however, no similar reaction occurred when VI was replaced by related furamides; no



VI VII

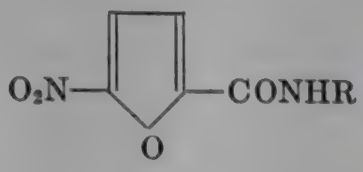
nitramide was obtained, and other nitration procedures led to extensive decomposition. Neither did 5-nitro-2-furohydroxamic acid, VIII (m.p. 169° (dec.)) give rise to an *exo*-nitro derivative under these conditions. VIII was prepared by condensation of 5-nitrofuroyl chloride with hydroxylamine; 5-nitro-2-furo-O-methylhydroxamate (m.p. 151–152°) and bis(5-nitro-2-furo)-O-methylhydroxamate (m.p. 105.6–106.0°) were similarly prepared using O-methylhydroxylamine.[60]



VIII

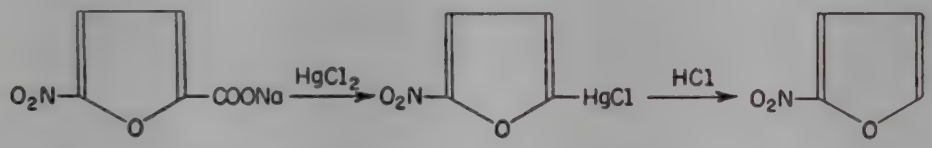
The carboxyl group of 5-nitro-2-furoic acid is easily replaced by —HgCl. Thus, treatment of the sodium salt with mercuric chloride produces 5-nitro-

TABLE 6. 5-NITRO-2-FURAMIDE AND ITS DERIVATIVES



R	M.p. (°C.)	Ref.
H	161	60, 8
CH_3	202–203	60
C_4H_9	89–90	60
C_6H_5	180	8
p-$CH_3C_6H_4$	162	8
o-HOC_6H_4	250	64
p-HOC_6H_4	143	64
p-$CH_3OC_6H_4$	183	64
p-ClC_6H_4	181	64
p-$NO_2C_6H_4$	255	64
2-Biphenyl	134–135	65
2-(4′-Carbethoxyamino)biphenyl	179–180	65
2-(4,4′-Biscarbethoxyamino)biphenyl	223–225	66

2-furylmercuric chloride (m.p. 208°) which may be cleaved with hydrochloric acid to 2-nitrofuran[37] (see also [67]).



Klinkhardt[1] reduced 5-nitro-2-furoic acid using tin and hydrochloric acid. The nucleus was destroyed under these conditions, and succinic acid was isolated as the product. In several instances, however, the nitro group has been successfully reduced to amine without attacking the ring. Thus, Marquis[68, 8] obtained ethyl 5-amino-2-furoate[c] by the action of aluminum amalgam on the nitro ester. It was his intention to convert the former to the free acid, and then, following decarboxylation, to obtain the elusive 2-furylamine. However, the amino ester could not be saponified without complete destruction, hence this approach proved fruitless.

Ethyl 5-nitro-2-furoate was reduced catalytically over platinum oxide

[c] Marquis[8] formulated the product as ethyl β-amino-2-furoate, since he had erroneously assigned the nitro group in the nitro ester to a β-position.

[64] Takahashi, Saikachi, Sasaki, Suzuki and Moritani, *J. Pharm. Soc. Japan*, **69**, 286 (1949); *C. A.*, **44**, 5372 (1950).

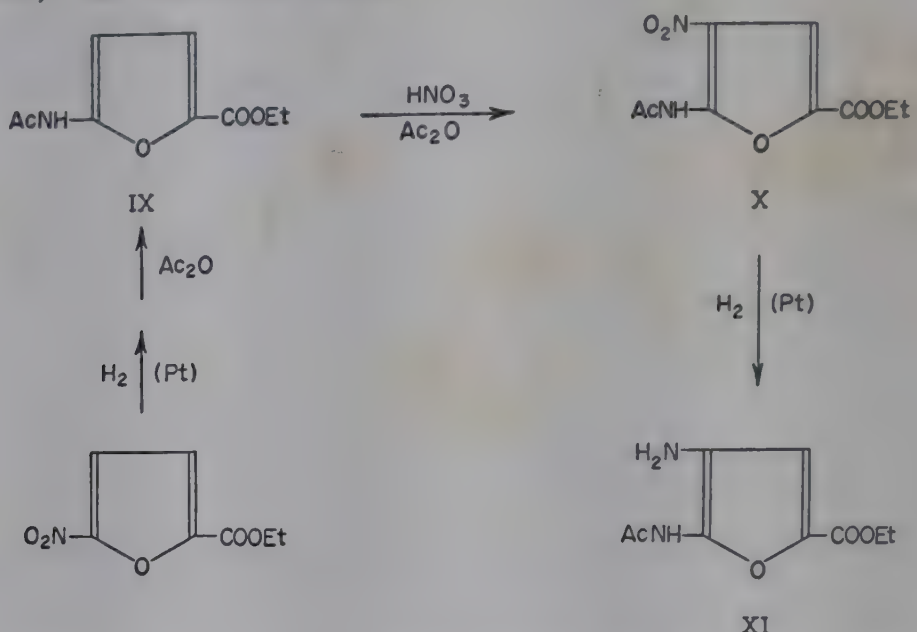
[65] Mamalis and Petrow, *J. Chem. Soc.*, **1950**, 703.

[66] Walls and Whittaker, *J. Chem. Soc.*, **1950**, 41.

[67] Burtner (to G. D. Searle and Co.), U. S. Pats. 2,206,804–5 (1940); *C. A.*, **34**, 7546 (1940).

[68] Marquis, *Compt. rend.*, **136**, 1454 (1903).

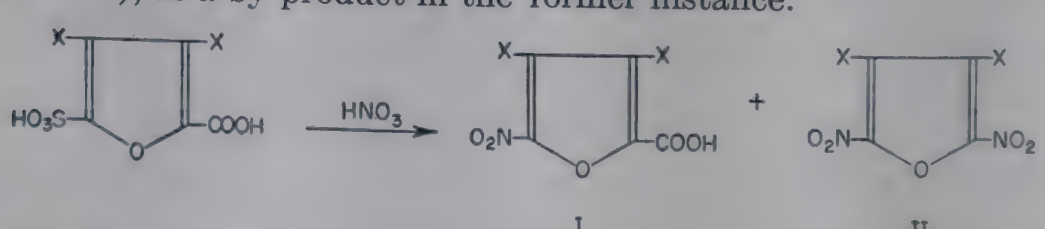
by Gilman and Wright[63] and by Rinkes,[21] who found this procedure more convenient than that employed by Marquis. Acetylation of the product gave rise to ethyl 5-acetamido-2-furoate, IX, which on subsequent nitration was transformed into ethyl 5-acetamido-4(or 3)-nitro-2-furoate, X.[63, 21] Catalytic reduction of X produced ethyl 5-acetamido-4(or 3)-amino-2-furoate, XI,[69] as illustrated below.



The properties of the several furylamines which have been mentioned are discussed elsewhere (p. 188).

Nitrohalofuroic Acids

The known nitrohalofuroic acids were obtained from the corresponding sulfohalo acids. As mentioned previously, α-sulfonic groups are readily removed during nitration with fuming nitric acid. In this way, 5-nitro-3,4-dibromo-(and dichloro)-2-furoic acids, I, were prepared from the corresponding sulfodihalo acids.[2, 70] As expected, some replacement-decarboxylation also occurred as evidenced by the isolation of 2,5-dinitro-3,4-dibromofuran, II, (X = Br), as a by-product in the former instance.

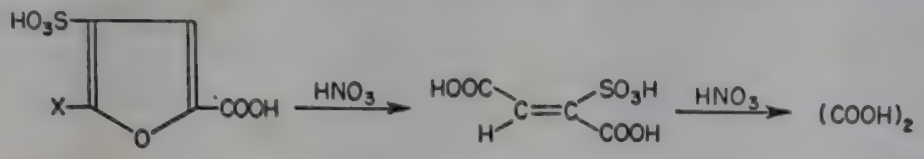


I II

Similar treatment of 5-sulfo-4-halo-2-furoic acids gave nitrohalofuroic acids in which it may be assumed that the nitro group occupies the 5-position.[2, 71]

[69] Gilman and Wright, *Rec. trav. chim.*, **53**, 13 (1934).
[70] Hill and Jackson, *Am. Chem. J.*, **12**, 112 (1890).
[71] Hill and Hendrickson, *Proc. Am. Acad. Arts Sci.*, **25**, 283 (1889).

Reaction failed, however, when applied to 5-halo-β-sulfo-2-furoic acids, III. No nitro acids were obtained. Instead, oxidation took place with the formation of sulfofumaric acid, IV, or under more drastic conditions, oxalic



III IV

acid [2, 71]. In view of the ease of decarboxylation of α-furancarboxylic acids during nitration, 2-nitro-5-halo-β-furansulfonic acid might have been expected as a product under the relatively mild temperature conditions employed in the preceding reaction. No such product was reported.

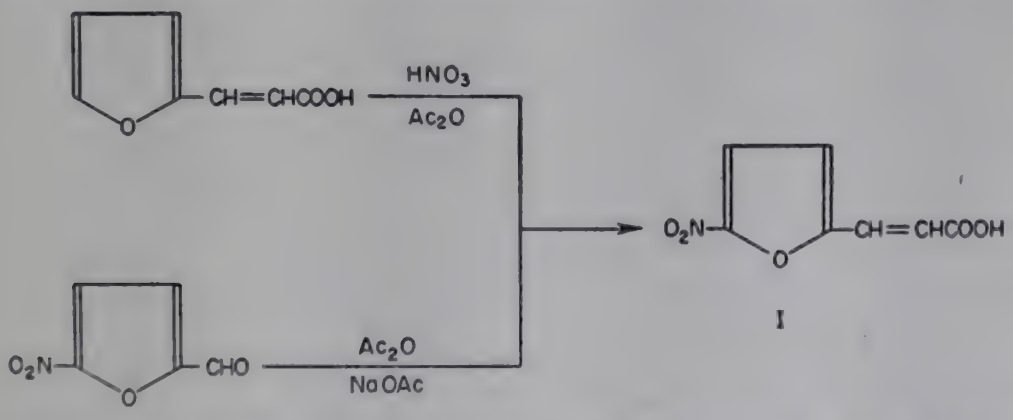
TABLE 7. NITROHALO-2-FUROIC ACIDS

Subst'd. 2-furoic acid	M.p. (°C.)	Ref.
4-Bromo-5-nitro*	159–160	2
3,4-Dibromo-5-nitro	204–205	2
4-Chloro-5-nitro*	140–141	71
3,4-Dichloro-5-nitro	189–190	72, 70

* Hill assigned the halogen atom to the 3-position (see Chapter 3).

3-(5-Nitro-2-furyl)acrylic Acid and Related Compounds

Nitration of 3-(2-furyl)acrylic acid and its esters introduces a nitro substituent into the 5-position to give 3-(5-nitro-2-furyl)acrylic acid, I, or the corresponding ester. The structure of I is known by its synthesis from 5-nitrofurfural by the Perkin condensation.[38] It is a very stable compound,



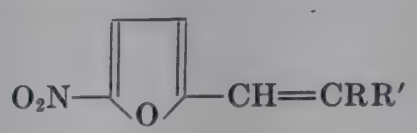
I

and is apparently unaffected by chromic acid. The ethyl ester of I is quite resistant to the action of thionyl chloride and phosphorus pentachloride. On heating with 65 per cent sulfuric acid it is hydrolyzed to the free acid. Decarboxylation of I, in quinoline, under the influence of powdered copper, gives rise to 2-nitro-5-vinylfuran.[25a]

[72] Hill and Jackson, *Proc. Am. Acad. Arts Sci.*, **24**, 360 (1888).

The related ethyl furfuralmalonate, $C_4H_3O—CH=C(COOEt)_2$, nitrates similarly to give the corresponding 5-nitro derivative, as shown by formation of the same product when 5-nitrofurfural is placed in reaction with ethyl malonate.[51, 5] It may be assumed, therefore, that the products obtained by Heuck[5] on nitration of furfuralmalonitrile and 2-cyano-3-(2-furyl)acrylic acid likewise possess the nitro substituent in the 5-position of the furan nucleus.

TABLE 8. 3-(5-NITRO-2-FURYL)ACRYLIC ACID AND RELATED TYPES



Compound			Derivatives (m.p., °C.)		Ref.
R	R′	M.p. (°C.)			
H	COOH	235–236	ethyl ester	125	38, 64
			acid chloride	92–94	
			amide	223	
			N-subst'd amides	see 64	
CN	COOH	250 (dec.)	ethyl ester	153 (dec.)	5
COOH	COOH	—	diethyl ester	108	51, 5
CN	CN	179 (dec.)	—		5

NITROFURANS AS CHEMOTHERAPEUTIC AGENTS

In 1944, Dodd and Stillman[73] conducted an investigation of the antibacterial activity of more than forty different furan compounds against *Staphylococcus aureus*, *Streptococcus hemolyticus* (*S. pyogenes*), *Diplococcus pneumoniae* (type I), *Eberthella typhosa*, *Escherichia coli*, and *Pseudomonas aeruginosa* (*Ps. pyocyanea*). They observed that the introduction of a nitro group into the 5-position of 2-substituted furan compounds conferred bacteriostatic properties against five of the six test organisms, which included both gram-positive and gram-negative bacteria. At certain levels of concentration, bactericidal activity was also noted (see also [74]).

On the basis of these results, Cramer and Dodd[48] studied the mode of antibacterial (*S. aureus*) action of six of the most promising nitrofurans (5-nitrofurfural semicarbazone, 5-nitrofuryl methyl ketone, 5-nitrofuroic acid and its *n*-propyl ester, 5-nitrofurfuryl propionate, and ethyl 3-(5-nitrofuryl)acrylate). 5-Nitrofurfural semicarbazone[75] was found to possess a unique type of bacteriostatic activity. It is markedly active during the

[73] Dodd and Stillman, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).
[74] Dodd, Hartmann and Ward, *Surg. Gynecol. Obstet.*, **83**, 73 (1946).
[75] Raffauf (to Eaton Laboratories, Inc.), U. S. Pat. 2,548,173 (1951).

lag phase of growth, greatly prolonging the period during which no bacterial reproduction takes place.[48, 76] Once initiated, however, the rate of reproduction is, thereafter, unaffected by the compound, which is available on the market under the trade name Furacin (brand of Nitrofurazone N. N. R.).

Furacin was the first of the nitrofuran series of compounds to display therapeutic activity when used in experimental infections (in mice) with various bacteria and trypanosomes[77] (see also [78]). For a review of the literature dealing with its use in clinical investigations, including the treatment of chronically infected wounds and other surface lesions, see Daily[79] (see also [80, 81, 82]). The drug is also effective against poultry coccidiosis (*Emeria tenella*) for which use it is marketed under the name NFZ (from Nitrofurazone).[83] Additionally, Green and Mudd[84] have shown that a variety of gram-positive and gram-negative organisms which were made resistant by repeated cultures in increasing concentrations of sulfathiazole, streptomycin and penicillin, were still as susceptible to Furacin as the original strains; no cross-resistance to the drug was encountered in these tests *in vitro*. For activity against viruses, see Eaton *et al.*[85]

A detailed investigation of the toxicity and pharmacology of Furacin was made by Krantz and Evans,[86] who report no toxic effect on heart action, blood pressure or respiration when administered to dogs in relatively large doses. The LD_{50} for mice is 380 mg./kg.[86] to 587 mg./kg.[77]; 590 mg./kg. for rats.[86] Four-tenths per cent of Furacin in the diet was fatal to rats; histologic sections showed marked changes in the structure of the liver and kidneys. Monkeys tolerated 300 mg. daily for five weeks with no significant pathologic effects. A number of human subjects consumed as much as 3–4 g. daily, and while about twenty per cent experienced nausea, blood and urine tests were normal. The use of Furacin is not devoid of hazards, however, the chief of which appears to be sensitization.[87, 88, 89, 90]

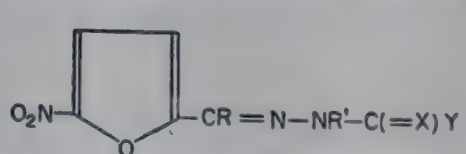
[76] Cramer, *J. Bact.*, **54**, 119 (1947).
[77] Dodd, *J. Pharmacol. Exptl. Therap.*, **86**, 311 (1946).
[78] Ziering and Buck, *Jubilee Vol. Emil Barell*, **1946**, 378; *C. A.*, **42**, 3533 (1948).
[79] Daily, *N. Y. State J. Med.*, **48**, 1386 (1948).
[80] Dreizen, Greene and Spies, *J. Dental Research*, **28**, 288 (1949); *Proc. Soc. Exptl. Biol. Med.*, **70**, 558 (1949).
[81] Hufstader, Anderson, Phatak and Snyder, *J. Dental Research*, **29**, 794 (1950).
[82] Stillman, Scott and Clampit (to Norwich Pharmacal Co.), U. S. Pat. 2,319,481 (1943); *C. A.*, **37**, 6413 (1943).
[83] Harwood and Stunz, *J. Parasitol.*, **35**, 175 (1949).
[84] Green and Mudd, *Proc. Soc. Exptl. Biol. Med.*, **64**, 57 (1947).
[85] Eaton, Huang and Levenson, *Proc. Soc. Exptl. Biol. Med.*, **71**, 501 (1949).
[86] Krantz and Evans, *J. Pharmacol. Exptl. Therap.*, **85**, 324 (1945).
[87] Hill and Flood, *Arch. Derm. Syph.*, **57**, 124 (1948).
[88] Morin, *J. Am. Med. Assoc.*, **133**, 963 (1947).
[89] Downing, Hanson and Lamb, *J. Am. Med. Assoc.*, **133**, 299 (1947).
[90] Downing, *New Engl. J. Med.*, **237**, 755 (1947).

For a study of the metabolism of nitrofurans, see Paul *et al.*,[91] who point out that those compounds which are metabolized to nitrofuroic acid exhibit little or no *in vivo* activity; that in general, the types which have shown chemotherapeutic action are at least partially resistant to metabolic breakdown and are excreted in the urine.

TABLE 9. SOME NITROFURAN COMPOUNDS, TOXICITY FOR NORMAL MICE AND THERAPEUTIC VALUE IN MICE INFECTED WITH HEMOLYTIC STREPTOCOCCI[92]

Compound (R = O_2N–furan–)	Toxicity	Therapy of *S. hemolyticus* infection		
	(LD_{50}, mg./kg.)	Dose (mg./kg.)	% Survival	Dosage/LD_{50}
$RCH{=}NNHCONH_2$ (Furacin)	750	150	67	1/5
$RC(CH_3){=}NNHCONH_2$	2000	1000	50	1/2
$RCH{=}NNHCOCONH_2$	2000	1000	80	1/2
$RCH{=}NN(CH_2CH_2OH)CONH_2$ (Furadroxyl)	600	300	40	1/2
$RCH{=}NNHCSNH_2$	1500	750	0	1/2
$(RCH{=}NNHC(NH)NH_2)_2 \cdot H_2SO_4$	400	200	10	1/2
$RC(CH_2OH){=}NNHCONH_2$	1500	750	90	1/2
$RCH{=}CHC(CH_3){=}NNHCONH_2$	3000	1000	30	1/3
$RCH{=}NNHCOCONHCH_2CH_2OH$	3000	1500	70	1/2
$RCH{=}NNHCOCH_2N(CH_3)_3Cl$	2000	1500	27	3/4
$RCH{=}NNHCOCH_3$	1500	750	15	1/2
$RCH{=}NN(CH_3)CONH_2$	500	250	10	1/2
$RCH{=}NNHCONHCH_3$	200	100	15	1/2

Intensive study of many nitrofuran types has revealed that only those possessing the structural arrangement, A, display therapeutic activity *in vivo*. The simplest compound of this class is Furacin (R = R′ = H; X = O;

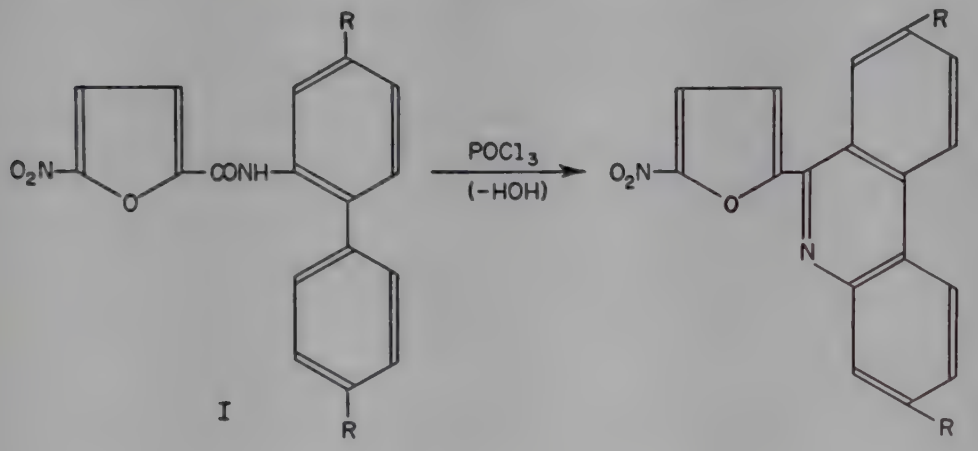


(A)

Y = NH_2), but a number of related types have been prepared and tested (Tables 3, 4 and 9) including the semicarbazones of 5-nitrofuryl methyl ketone and the corresponding hydroxymethyl ketone[92] (see also [55, 58]). Activity was observed where R = hydrogen, alkyl, or hydroxymethyl; R′ = alkyl or hydroxyalkyl; X = oxygen, sulfur or imino; Y = alkyl, hydroxyalkyl, alkoxy, amido, alkylamido, carbamido, carboxyalkyl, guanido, carbamyl, or hydroxyalkylcarbamyl. Of all of these, however, Furacin

[91] Paul, Austin, Paul and Ells, *J. Biol. Chem.*, **180**, 345 (1949).
[92] Dodd, Cramer and Ward, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 313 (1950).

was observed to be the outstanding member of the series. No other substitution in position 2 or 5 reproduced the activity of this drug. Neither could the effect be duplicated by replacing the furan nucleus with thiophene or pyrrole systems. Few β-nitrofuran derivatives have been tested, but the indications are that such types do not hold the same promise as the α-nitro compounds.[92] For additional work on bacteriostatically (*in vitro*) active α-nitrofuran types the reader is referred to Takahashi *et al.*[53, 64] and to Dann and Möller.[36] For the activity of 5-nitro-3-furaldehyde semicarbazone (isomer of Furacin), see Hayes.[50] Additionally, 6-(5-nitrofuryl)phenanthridines, II, of potential trypanocidal value have been described recently by Walls and Whittaker[66] and by Mamalis and Petrow.[65] Synthesis involved cyclodehydration of the appropriate 2-(5-nitrofuramido)biphenyl, I (see Table 6), by the action of phosphorus oxychloride.



(Nitroalkenyl)furans and (Nitroalkyl)furans

The known furylnitroölefins (Table 10) have been prepared, for the most part, by condensation of furfural with nitroparaffins in the presence of a basic condensing agent at low temperature (see also p. 269). They readily form salts with alkali or alkali soaps,[93, 94] but are decomposed on warming

$$C_4H_3O{-}CHO + RCH_2NO_2 \xrightarrow{-HOH} C_4H_3O{-}CH{=}CRNO_2$$

with alkali, presumably by a mechanism similar to that operative with the α-nitrofurans, of which they are vinylogs.

Reduction gives rise to the appropriate aldoxime or ketoxime, and has been accomplished using aluminum amalgam,[95] zinc and acetic acid,[96, 94]

[93] Wolfrom, Report OSRD No. 1568, National Defense Research Committee of Office of Scientific Research and Development, 1943.

[94] Kasiwagi, *Bull. Chem. Soc. Japan*, **2**, 110 (1927); *C. A.*, **21**, 2895 (1927).

[95] Yabuta and Kambe, *Proc. Imp. Acad. Tokyo*, **4**, 120 (1928); *C. A.*, **22**, 4503 (1928).

[96] Bouveault and Wahl, *Bull. soc. chim.* (3), **29**, 521 (1903).

iron turnings and hydrochloric acid[97]; also electrolytically,[98, 99] and catalytically with palladium on charcoal.[100]

Sodium bisulfite adds to ω-nitrovinylfuran (1-nitro-2-(2-furyl)ethylene), I, to form sodium 1-nitro-2-furylethanesulfonate, II (syrup) which on reduction gave rise to the corresponding amino sulfonate, III, m.p. 250–252° (dec.)[101] (see also [102, 103]).

$$C_4H_3O{-}CH{=}CHNO_2 \xrightarrow{NaHSO_3} C_4H_3O{-}CH(SO_3Na)CH_2NO_2$$

I

II

(H)

$$C_4H_3O{-}CH(SO_3Na)CH_2NH_2$$

III

The Grignard reagent likewise adds normally to the furylnitroölefins to produce 2-(nitroalkyl)furan types. Thus, interaction of butylmagnesium bromide with I gives rise to 2-(1-nitro-2-hexyl)furan, IV, b.p. 78–82° (0.4 mm.).[104, 105] On the other hand, Reichert and Kuhn[100] report failure of an attempt to add the elements of methanol to 2-(2-phenyl-2-nitrovinyl)-furan under conditions which brought about such addition to ω-nitrosty-

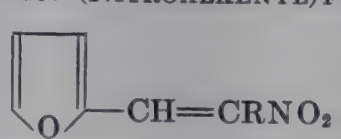
$$I \xrightarrow{BuMgBr} C_4H_3O{-}CH(C_4H_9)CH_2NO_2$$

IV

renes.

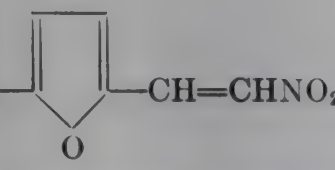
Cautious nitration of I introduces a nitro group at the 5-position as shown by oxidation of the product (m.p. 143–144°) to 5-nitrofuroic acid by the action of chromic acid.[4] For the hydrolytic cleavage of I by heating with strong hydrochloric acid, see Chapter 14.

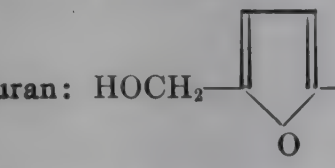
TABLE 10. (NITROALKENYL)FURANS



R	Physical constants (°C.)	Ref.
H	b.p. 111 (4 mm.), 135 (20 mm.) m.p. 74–75	4, 108, 96, 94, 95, 109, 93, 107; see also 110, 25
CH_3	m.p. 48–49	94, 93, 97
C_2H_5	b.p. 124–125 (10 mm.), 130–131 (13 mm.) d_4^{20} 1.1626; n_D^{20} 1.6070	111, 97
n-C_3H_7	b.p. 136–137 (13 mm.) d_4^{20} 1.1254; n_D^{20} 1.5902	111, 97
i-C_3H_7	b.p. 121–122 (13 mm.)	111
i-C_4H_9	b.p. 137–138 (12 mm.)	111
C_6H_5	m.p. 87–87.5	94, 100
o-ClC_6H_4	m.p. 101.1	112

For the fungistatic activity of furylnitroölefins, see McGowan *et al.*[106] (see also [107]).

5-Methyl-2-(2-nitrovinyl)furan:  m.p. 75–76°; from 5-methylfurfural and nitromethane in aqueous potassium hydroxide. Compound was reduced (Zn-AcOH) to the oxime of 5-methyl-2-furylacetaldehyde which was dehydrated to the corresponding nitrile, 5-methyl-2-furylacetonitrile.[113]

5-(Hydroxymethyl)-2-(2-nitrovinyl)furan:  no constants. Prepared and tested for fungistatic activity.[106]

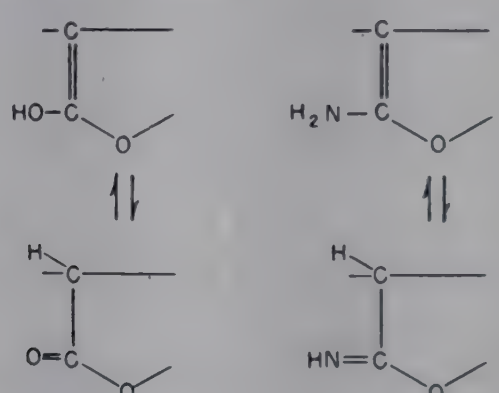
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[97] Hass, Susie and Heider, *J. Org. Chem.*, **15,** 8 (1950).
[98] Takamoto, *J. Pharm. Soc. Japan*, **48,** 136 (1928); *C. A.*, **22,** 2354 (1928).
[99] Takamoto, *J. Pharm. Soc. Japan*, **48,** 366 (1928); *C. A.*, **22,** 3162 (1928).
[100] Reichert and Kuhn, *Ber.*, **74,** 328 (1941).
[101] Heath and Piggott, *J. Chem. Soc.*, **1947,** 1481.
[102] Thurston (to American Cyanamid Co.), U. S. Pat. 2,372,233 (1945); *C. A.*, **39,** 5023 (1945); Brit. Pat. 592,747 (1947); *C. A.*, **42,** 2283 (1948).
[103] Thurston (to American Cyanamid Co.), U. S. Pat. 2,385,314 (1945); *C. A.*, **40,** 609 (1946); U. S. Pats. 2,402,510–4 (1946); *C. A.*, **41,** 158 (1947).
[104] Buckley and Ellery, *J. Chem. Soc.*, **1947,** 1497.
[105] Buckley (to Imperial Chemical Industries Ltd.), U. S. Pat. 2,408,607 (1946); *C. A.*, **41,** 1232 (1947).
[106] McGowan, Brian and Hemming, *Applied Biol.*, **35,** 25 (1948).
[107] Bousquet, Kirby and Searle (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,335,384 (1943); *C. A.*, **38,** 2834 (1944).
[108] Thiele and Landers, *Ann.*, **369,** 300 (1909).
[109] Fujise, Takeuchi, Kamioka and Tiba, *Ber.*, **68,** 1272 (1935).
[110] Runde, Scott and Johnson, *J. Am. Chem. Soc.*, **52,** 1284 (1930).
[111] Kanao, *J. Pharm. Soc. Japan.* **550,** 1019 (1927); *C. A.*, **22,** 1588 (1928).
[112] Bahner, Dickson and Moore, *J. Am. Chem. Soc.*, **70,** 1982 (1948).
[113] Scott and Johnson, *J. Am. Chem. Soc.*, **54,** 2549 (1932).

Chapter 5

FURANOLS AND FURYLAMINES

In large measure, attempts to synthesize the simple furan analogs of the phenols and aromatic amines have been frustrating, yet quite revealing in some respects with regard to an over-all understanding of the furan heterocycle. The extensive chemistry of these benzene types is almost entirely missing in the furan series, and with the exception of the findings reported in one very controversial investigation, the free furanols and furylamines which have been studied bear only a superficial resemblance to their aromatic prototypes; they more closely approximate the properties associated with aliphatic keto-enol and ketimine-eneamine systems, respectively. Evidence for keto-enol tautomerism in the case of the related 2-thienol has been presented by Hurd and Kreuz.[1]



As a consequence of the nuclear oxygen atom, the "keto" and "ketimine" tautomers of the furanols and furylamines, respectively, can be seen to possess the familiar groupings of esters and imido esters, directly so in the case of alpha substituted types (above), and by vinylogy where the substituent is attached to a beta carbon of the nucleus. As will be shown, this is reflected in the properties of the compounds which have been studied.

Furanols and Related Compounds

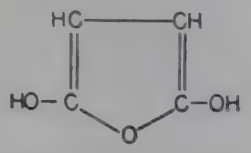
A number of furyl ethers and esters have been described, but evidence for the existence of the furanols themselves is largely confined to a few heavily substituted types,[a] and to reactions in solution. Structural considerations have led a majority of investigators to study the β-furanols rather

[a] For the possible formation of 5-hydroxyfurfural and 5-hydroxy-2-furoic acid by oxidation of furfural, see p. 391.

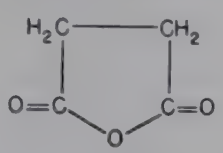
[1] Hurd and Kreuz, *J. Am. Chem. Soc.*, **72**, 5543 (1950).

than the α-isomers, it being anticipated that the former would exhibit greater stability in the enolic form. To a limited extent this expectation has been realized, but the available information indicates that, in both instances, there is a very pronounced tendency for the furanols to tautomerize to the corresponding furanone. In the case of an α-furanol, the latter is, in reality, a γ-lactone, and is subject to the cleavage reactions common to this class of compounds. This behavior reveals the lesser degree of aromatic character of the furan ring compared to that of benzene,[b] the simple hydroxy derivatives of which are particularly noted for their reactions in the enolic form.

The hypothetical compound, 2,5-furandiol, I, may be considered to be the enolic form of succinic anhydride, II. Its properties, however, are satisfactorily described by the anhydride structure; experimental evidence for structure I is entirely lacking. Similarly, the chemistry of 3-pentenoic γ-

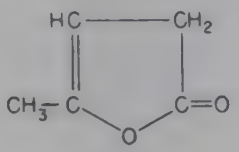


I

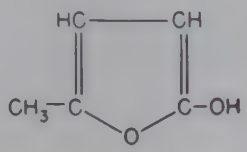


II

lactone (so-called α-angelica lactone), III, offers little support for the existence of the enolic modification, 5-methyl-2-furanol, IV, beyond the fact that a Zerewitinoff determination liberates some methane; approximately one-third of a mole of methane was obtained per mole of the lactone.[3] Furthermore, while alkoxy[c] derivatives related to IV have been prepared by indirect means, they lack the stability of the phenolic ethers. Thus, Ushakov



III



IV

and Kucherov[5] obtained 5-(diphenylmethyl)-2-methoxyfuran, VI (m.p. 132–132.5°) by the action of methanolic hydrogen chloride on the methyl ether of diphenylfurylcarbinol, V. VI, which may be looked upon as a ketene acetal, is readily hydrolyzed by aqueous hydrochloric acid to 5,5-

[b] Thiophene compounds generally bear a closer resemblance to their benzene analogs than do the corresponding furan types. 2-Thienol and substituted thienols have been shown to exist in tautomeric forms.[1, 2]

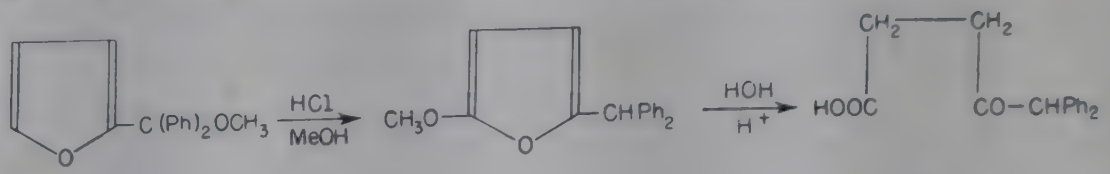
[c] What may have been the benzoic ester of 3, 4, 5-triphenyl-2-furanol is described by Pütter and Dilthey.[4]

[2] Steinkopf and Thormann, *Ann.*, **540**, 1 (1939).

[3] Langlois and Wolff, *J. Am. Chem. Soc.*, **70**, 2624 (1948).

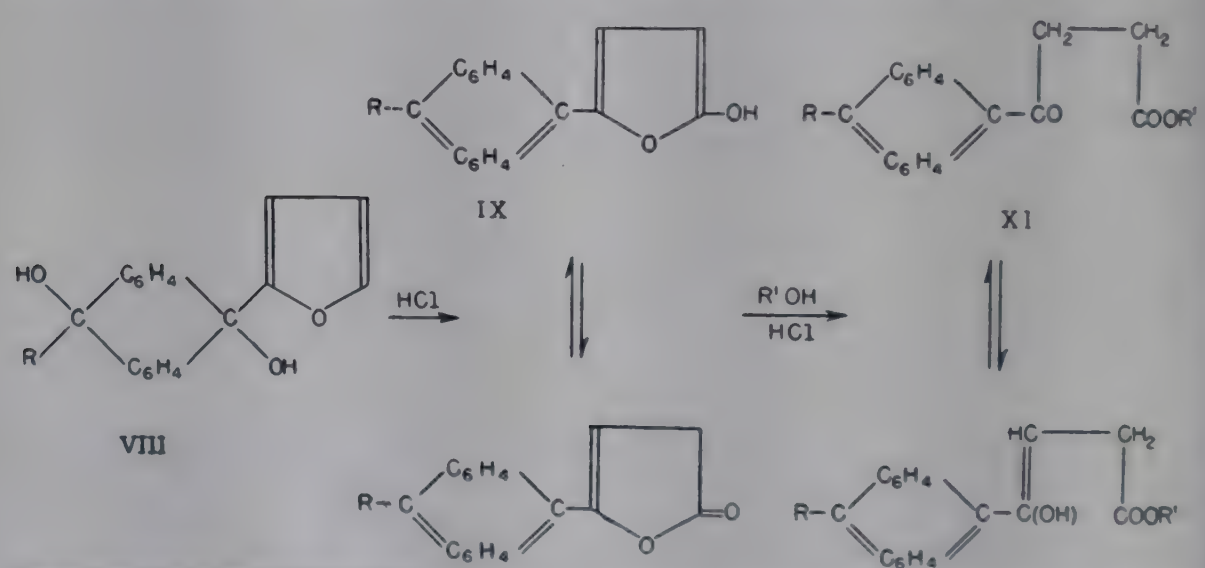
[4] Pütter and Dilthey, *J. prakt. Chem.*, **149**, 183 (1937).

diphenyllevulinic acid, VII (see p. 645). Accordingly, the property responsible for the retention of nuclear configuration which is so characteristic of benzene types including the phenols and their derivatives, appears to be completely lacking in the α-furanols and their ethers.



V VI VII

Additional evidence in support of the lactonic rather than enolic configuration for α-furanols is seen in the work of Étienne and Brisson[6, 7, 8] who were concerned with the properties of 9-furyl-10-phenyl-9,10-dihydro-9,10-anthracene diol, VIII (R = Ph), and the related difuryl compound (VIII, R = C_4H_3O) (see p. 651). Treatment with hydrochloric acid gave rise to crystalline products, formulated as 5-(10-phenyl-9-anthryl)-2-furanol, IX (R = Ph), m.p. 248°, and IX (R = C_4H_3O), m.p. 168°, respectively.[d] On the basis of the behavior of these products toward alkali, and toward alcohol and hydrochloric acid, however, the tautomeric 3-butenoic lactone structure, X, would appear to be the stable form. These reagents cleave the ring with formation of carboxylic salts and esters (XI), respectively, as outlined below. Borsche[9, 10] (see also [11]) likewise prefers the lactone con-



VIII IX XI

[d] An explanation of these transformations is offered elsewhere (p. 651).

[5] Ushakov and Kucherov, *J. Gen. Chem. U. S. S. R.*, **14**, 1073 (1944); *C. A.*, **40**, 7185 (1946).

[6] Étienne and Brisson, *Compt. rend.*, **224**, 1775 (1947).

[7] Étienne and Brisson, *Compt. rend.*, **227**, 208, 288 (1948).

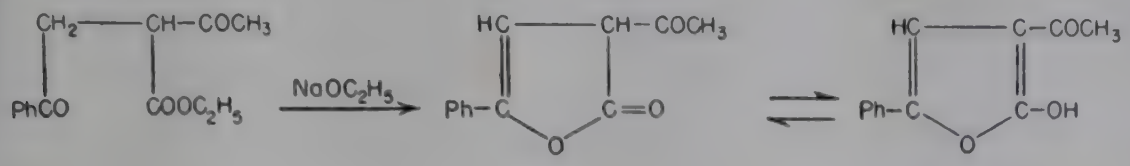
[8] Brisson, *Compt. rend.*, **227**, 1103 (1948).

[9] Borsche and Fels, *Ber.*, **39**, 1809, 1922 (1906).

[10] Borsche and Spannagel, *Ann.*, **331**, 298 (1904).

[11] Wilds and Johnson, *J. Am. Chem. Soc.*, **67**, 286 (1945).

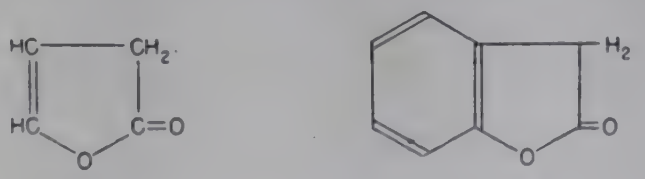
figuration, XII, rather than the corresponding α-furanol form, XIII, for the compound obtained by the action of sodium ethoxide on phenacylacetoacetic ester.



XII XIII

It is surprising, therefore, to find reports by Hodgson and Davies[12, 13] attributing definite phenolic characteristics to the compound which they formulated as 2-furanol, XIV. To date there has been no confirmation of their findings which, in many respects, are so unprecedented as to be of questionable validity. The simple furanol is described as a colorless, crystalline compound, m.p. 80° (dec. 90°), and was obtained by heating (200°) 5-sulfo-2-furoic acid with strong, aqueous sodium hydroxide in the presence of a small amount of potassium chlorate. Elemental analyses were satisfactory for XIV, it being assumed that the product was a C_4 compound. Failure to reduce ammoniacal silver nitrate solution was cited in support of the furanol structure; as evidence that the tautomeric lactone form[e] is not readily assumed. Hodgson and Davies report the successful nitration of XIV using nitric-sulfuric mixed acid.[f] The product, m.p. 92°, was formulated as 5-nitro-2-furanol, XV, and was identical to that obtained from the corresponding nitroso compound, XVI (m.p. 176°), by oxidation with potassium ferricyanide. XV (also XVI) was dissolved in aqueous

[e] By comparison with 2-thienol,[1] XIV would be expected to exist in equilibrium with the "keto" tautomer, 3-butenoic γ-lactone, XIV A; largely in the latter form by comparison with III and IV (above). In this respect it is interesting to point out that the reactions of the related coumaran-2-one (*o*-hydroxyphenylacetic lactone)



XIV A XIV B

are, for the most part, consistent with the lactone configuration, XIV B; this despite the fact that the furan ring is fused to a benzene nucleus, which might have been expected to stabilize the enol tautomer.

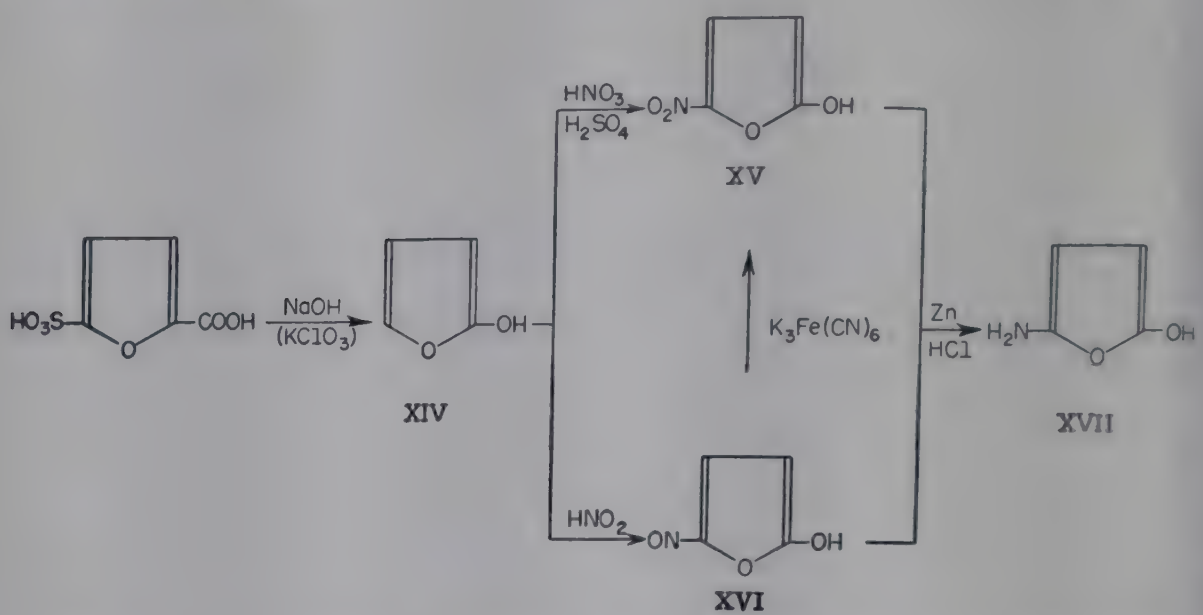
[f] Nitration with this vigorous reagent had formerly been carried out only with furans possessing strongly electron-withdrawing substituents[14] (p. 157). That an otherwise unsubstituted hydroxyfuran (XIV) could withstand this reagent is difficult to reconcile with the experience of other investigators.

[12] Hodgson and Davies, *J. Chem. Soc.*, **1939**, 806.

[13] Hodgson and Davies, *J. Chem. Soc.*, **1939**, 1013.

[14] Hill and White, *Am. Chem. J.*, **27**, 193 (1902).

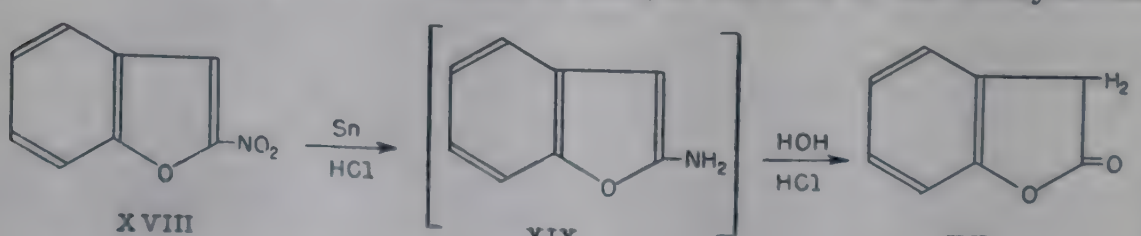
sodium hydroxide,[g] and subsequently reduced to a reputedly stable 5-amino-2-furanol, XVII (m.p. 185°) by the action of zinc and hydrochloric acid.[h] The reactions involved are illustrated below. A reinvestigation is very much in order.



Also of a controversial nature is the reported synthesis of 3-furanol, XXII; colorless needles, m.p. 58°.[12, 13] Despite numerous trials, Bailey and Waggoner[18] were unable to reproduce the first step in its preparation,

[g] Nitrofurans, particularly those wherein the nitro substituent is located on an α-carbon atom of the nucleus, are notoriously unstable toward alkalies (Chapter 4, Chapter 14). This reported stability of XV toward aqueous sodium hydroxide is completely at variance with the findings of other workers.

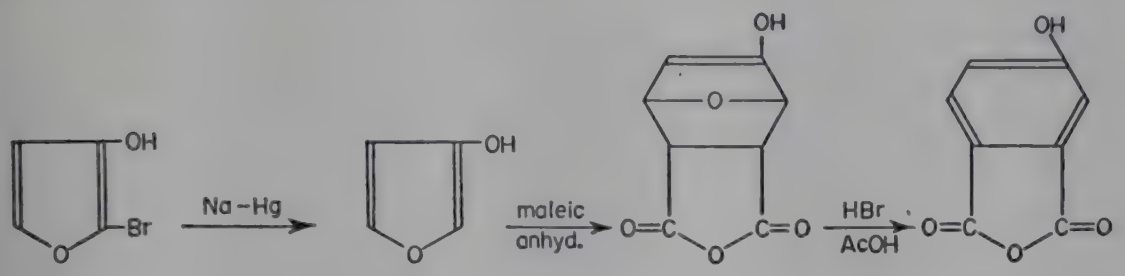
[h] It is inconceivable that the product, XVII, could exist under these conditions. If formed at all, it would be expected to undergo facile cleavage and deamination. This is the usual experience with furylamines (p. 183), and also with the related benzofuran types, the properties of which should more nearly approximate those of the aromatic amines. For example, reduction of 2-nitrobenzofuran, XVIII, using tin and hydrochloric acid, gives rise to *o*-hydroxyphenylacetic lactone, XX, and not the amino derivative, XIX.[15, 16] Similarly XIX, in the form of the methylurethan



undergoes hydrolytic deamination to XX when treated with aqueous hydrochloric acid.[17]

[15] Stoermer *et al.*, *Ber.*, **30**, 2094 (1897); **34**, 1806 (1901); **35**, 1640 (1902).
[16] Czaplicki, *Ber.*, **42**, 828 (1909).
[17] Rinkes, *Rec. trav. chim.*, **51**, 349 (1932).
[18] Bailey and Waggoner, *J. Org. Chem.*, **15**, 159 (1950).

involving treatment of 2-furoic acid with aqueous bromine under carefully specified conditions to obtain what Hodgson and Davies formulated as 2-bromo-3-furanol, XXI (m.p. 85°). Following reduction of XXI to XXII with sodium amalgam, the English investigators report subsequent preparation of 2-nitro-3-furanol (m.p. 76°), and 2-amino-3-furanol (m.p. 92°) by the techniques discussed previously. Additionally, they offer a proof of structure for XXII; the maleic anhydride adduct,[i] XXIII, was converted into the known 4-hydroxyphthalic anhydride, XXIV. This work must be viewed with skepticism, not alone because of the experience of Bailey and



XXI XXII XXIII XXIV

Waggoner but, as will be seen, the implied stability of XXII is inconsistent with the properties reported for other β-furanol types which have been studied.

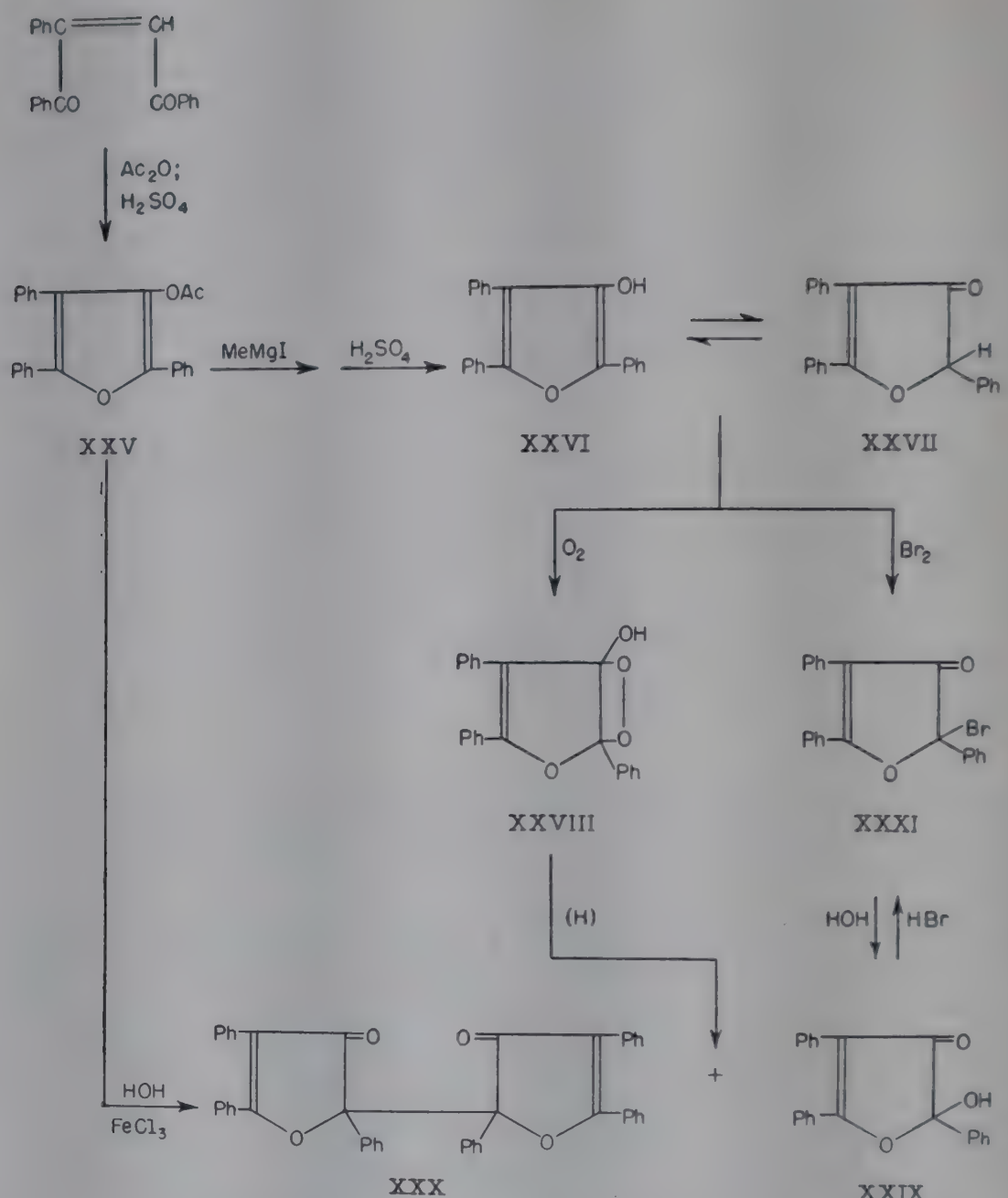
For example, while several highly arylated β-furanols have been shown to exist, as evidenced by reactions in solution, it has not been possible to effect isolation in the enolic form. 2,4,5-Triphenyl-3-furyl acetate, XXV, obtained by the action of acetic anhydride on 1,3,4-triphenyl-2-buten-1,4-dione in the presence of sulfuric acid,[j] gives rise to the furanol, XXVI on acid-hydrolysis, but the latter ketonizes readily, and on working up the reaction mixture the tautomeric furanone, XXVII (m.p. 112°) is obtained.[20] XXVI was obtained, in solution, by treating XXV with methylmagnesium iodide, followed by careful acidification with sulfuric acid in an atmosphere of nitrogen. The latter precaution is vital in all reactions with XXVI because of the readiness with which it reacts with oxygen to form a

[i] The supposed 2-furanol would not react with maleic anhydride.[12, 13]

[j] Most of the known 3-acyloxyfurans (Table 1) were synthesized from related unsaturated 1,4-diketones by this procedure. For the proposed mechanism of this reaction, see Lutz and McGinn.[19]

[19] Lutz and McGinn, *J. Am. Chem. Soc.*, **64**, 2585 (1942).

[20] Kohler, Westheimer and Tishler, *J. Am. Chem. Soc.*, **58**, 264 (1936).



peroxide which Kohler[20] has formulated as XXVIII. In the presence of alkali, or on reduction (AcOH-Zn; H_2-Pt), the peroxide is transformed into the hydroxyfuranone,[k] XXIX (m.p. 191°), together with the bimolecular

[k] The interesting chemistry of the hydroxyfuranones and their derivatives is considered to be beyond the scope of this monograph. For discussion of this type of dihydrofuran, especially with regard to possible ring-chain tautomerism, the reader is referred to the following published work:[20, 21, 22, 23, 24, 25, 19, 26, 27] (see also [28]).

[21] Kohler and Woodward, *J. Am. Chem. Soc.*, **58**, 1933 (1936).
[22] Lutz and Stuart, *J. Am. Chem. Soc.*, **59**, 2316, 2322 (1937).
[23] Lutz and Smith, *J. Am. Chem. Soc.*, **61**, 1465 (1939).
[24] Lutz and Smith, *J. Am. Chem. Soc.*, **63**, 1148 (1941).
[25] Lutz, Smith and Stuart, *J. Am. Chem. Soc.*, **63**, 1143 (1941).
[26] Lutz and McGinn, *J. Am. Chem. Soc.*, **65**, 849 (1943).
[27] Lutz, Amacker, King and Shearer, *J. Org. Chem.*, **15**, 181 (1950).
[28] Blatt, *J. Am. Chem. Soc.*, **57**, 1103 (1935); **58**, 1894 (1936).

compound, XXX (m.p. 272–274°). XXIX and the corresponding bromofuranone, XXXI (m.p. 154°) are interconvertible as illustrated above. When shaken with copper, XXXI undergoes a coupling reaction to form

TABLE 1. SOME β-FURYL ETHERS AND ESTERS

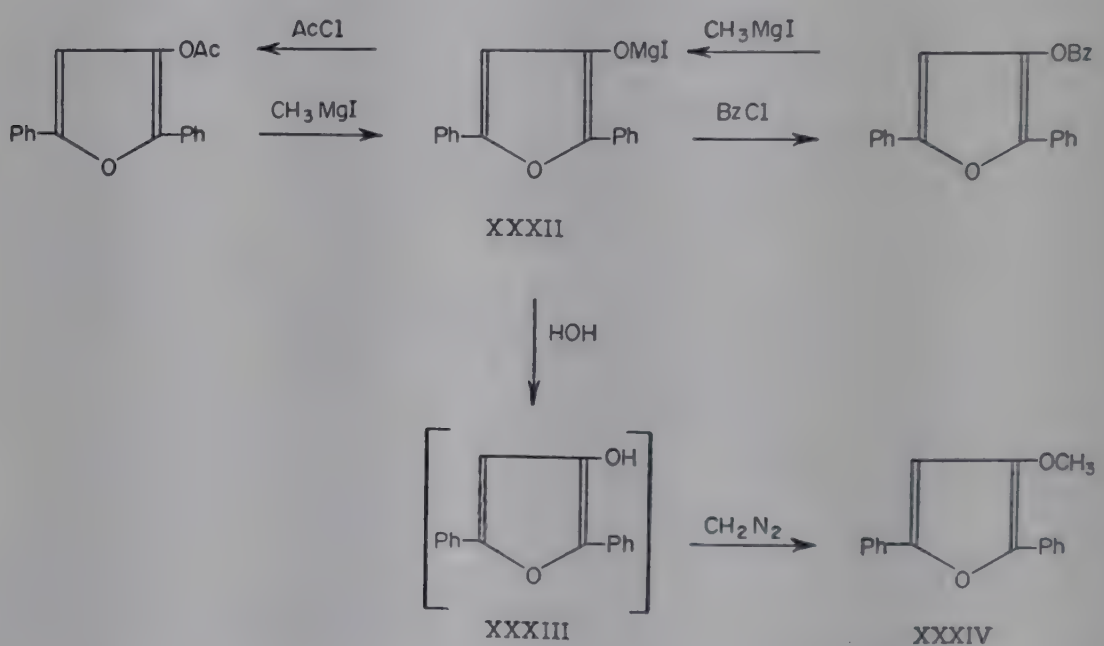


R	R′	R″	R‴	M.p. (°C.)	Ref.
CH_3	H	C_6H_5	C_6H_5	113–115	30, 31, 32, 29
C_2H_5	H	C_6H_5	C_6H_5	94–95	30
n-C_3H_7	H	C_6H_5	C_6H_5	86–87	33, 34
i-C_3H_7	H	C_6H_5	C_6H_5	87–88	30
n-C_4H_9	H	C_6H_5	C_6H_5	60–61	34
i-C_4H_9	H	C_6H_5	C_6H_5	71–72	33, 34
CH_3OCH_2(?)	H	C_6H_5	C_6H_5	75–75.5	29
C_6H_5	H	C_6H_5	C_6H_5	91	35
p-$CH_3C_6H_4$	H	C_6H_5	C_6H_5	113	35
CH_3	H	*p*-ClC_6H_4	*p*-ClC_6H_4	114	35
CH_3	H	*p*-BrC_6H_4	*p*-BrC_6H_4	113	35
CH_3	H	mesityl	mesityl	90–91	26
CH_3CO	H	C_6H_5	C_6H_5	95	36, 21; see also 37, 29, 34
C_6H_5CO	H	C_6H_5	C_6H_5	139–140	29; see also 24
CH_3CO	H	*p*-$CH_3C_6H_4$	*p*-$CH_3C_6H_4$	100.5	36
CH_3CO	H	mesityl	mesityl	100–101	38, 39, 26
C_6H_5CO	H	mesityl	mesityl	116–116.5	26
CH_3CO	CH_3	C_6H_5	C_6H_5	94–95	19, 29
C_6H_5CO	CH_3	C_6H_5	C_6H_5	129.5–130	29
CH_3CO	CH_3	mesityl	mesityl	88	40
CH_3CO	C_6H_5	C_6H_5	*t*-C_4H_9	99–100	41
CH_3CO	C_6H_5	C_6H_5	C_6H_5	137–138	20, 29; see also 42
CH_3CO	mesityl	C_6H_5	C_6H_5	124.5–126.5	43

[29] Lutz, McGinn and Bailey, *J. Am. Chem. Soc.*, **65**, 843 (1943).
[30] Bailey and Lutz, *J. Am. Chem. Soc.*, **69**, 498 (1947).
[31] Conant and Lutz, *J. Am. Chem. Soc.*, **47**, 881 (1925).
[32] Lutz and Palmer, *J. Am. Chem. Soc.*, **57**, 1957 (1935).
[33] Bailey and Kelly, *J. Am. Chem. Soc.*, **70**, 3442 (1948).
[34] Bailey and Christian, *J. Am. Chem. Soc.*, **71**, 4122 (1949).
[35] Lutz, *J. Am. Chem. Soc.*, **51**, 3008 (1929).
[36] Lutz, *J. Am. Chem. Soc.*, **48**, 2916 (1926).
[37] Lutz and Wilder, *J. Am. Chem. Soc.*, **56**, 2065 (1934).
[38] Lutz and Wood, *J. Am. Chem. Soc.*, **60**, 229, 705 (1938).
[39] Lutz, Reveley and Mattox, *J. Am. Chem. Soc.*, **63**, 3171 (1941).
[40] Lutz and Terry, *J. Am. Chem. Soc.*, **64**, 2426 (1942).
[41] Japp and Maitland, *J. Chem. Soc.*, **85**, 1496 (1904).
[42] Thiele, *Ber.*, **31**, 1247 (1898).
[43] Lutz and Kibler, *J. Am. Chem. Soc.*, **61**, 3007 (1939).

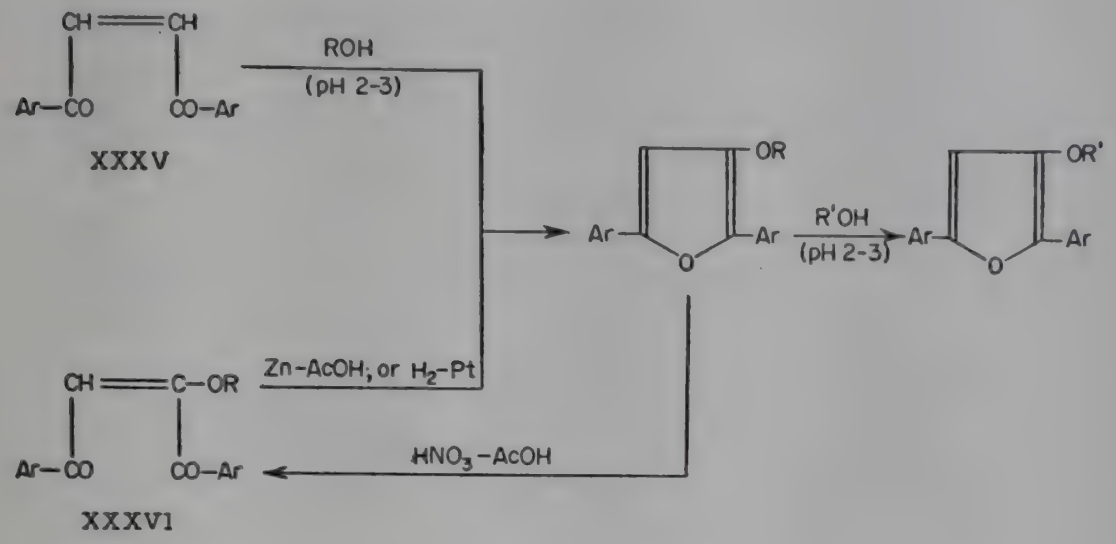
XXX,[20] which may also be obtained by hydrolysis of XXV in the presence of an oxidizing agent such as ferric chloride.[29] Subsequent work by Kohler and Woodward[21] revealed that the less highly phenylated 2,5-diphenyl-3-furanol behaved like XXVI, and it was concluded that the β-furanols are more akin to the aliphatic enols than to the phenols.

Others, notably Lutz and his students, have carried out related studies and have described a number of β-furyl esters and ethers (Table 1). Where attempted, isolation of the free furanols has been uniformly unsuccessful. It has been observed, however, that the iodomagnesium enolate, XXXII, of 2,5-diphenyl-3-furanol, XXXIII, can be acylated with acetyl and benzoyl chlorides to obtain the appropriate esters.[29] On the other hand, XXXII does not react normally when alkylation is attempted with methyl iodide or methyl sulfate, although the methyl ether, XXXIV, was obtained in low yield by the action of diazomethane on an ethereal solution of the free furanol.



Two more or less general methods have been employed for the synthesis of β-furyl ethers from non-furan types. These involve (1) addition of an alcohol to appropriate unsaturated 1,4-diketones, XXXV, under carefully controlled acidic conditions, and (2) reduction of alkoxy derivatives, XXXVI, of these diketones as outlined below.[30, 31] Some of the limitations of the first procedure have been brought to light recently by Bailey,[33, 34] who also observed that the ethers undergo trans-etherification when subjected to the action of an alcohol in the presence of a trace of hydrogen chloride, or preferably the latter and triethylammonium chloride. In this

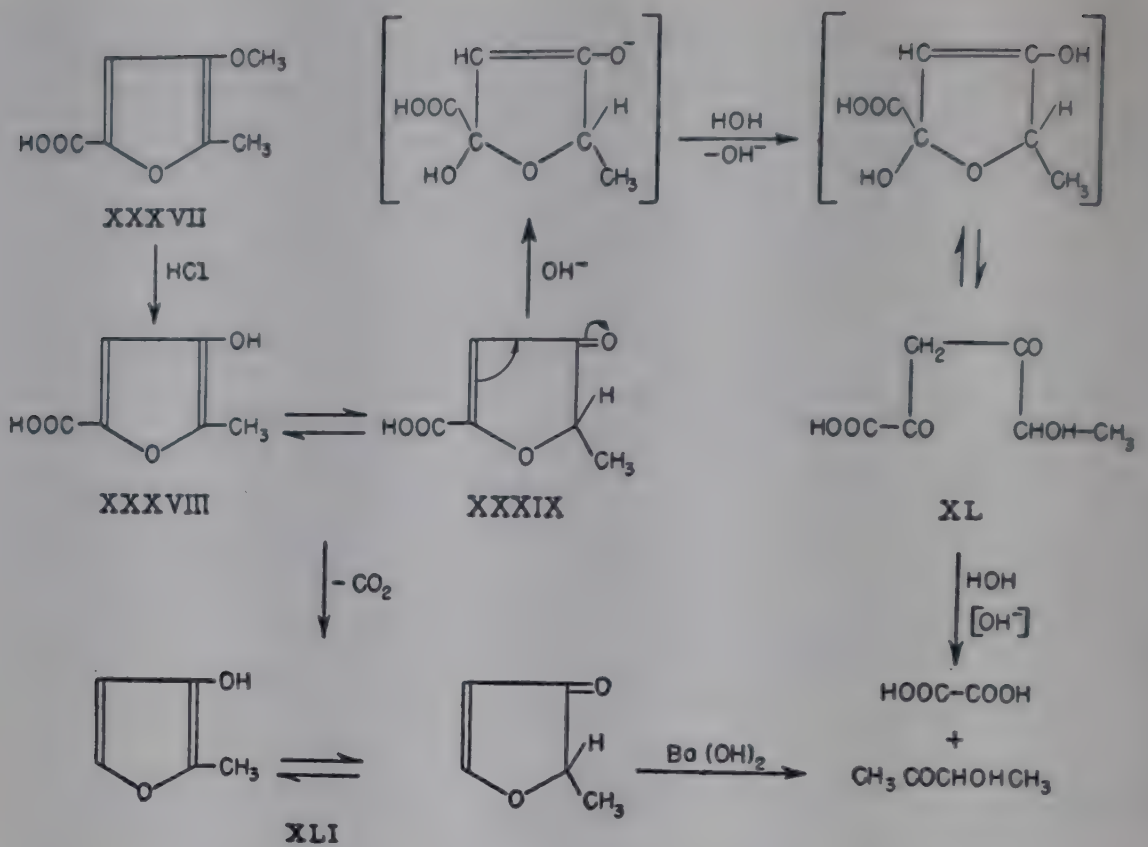
way, it is possible to effect conversion of one β-alkoxyfuran into another. The characteristic oxidation of 2,5-diarylfurans with nitric acid to form *cis* unsaturated 1,4-diketones (p. 49) is also applicable to 2,5-diaryl-3-furyl ethers, which are thereby transformed into the corresponding *cis*-1,4-diaryl-2-alkoxy-2-buten-1,4-dione, XXXVI.[34]



Votoček and Malachta[44, 45] obtained 4-methoxy-5-methyl-2-furoic acid, XXXVII (m.p. 158°) by treating a suspension of 5-ketorhamnonic lactone in methanol with dry hydrogen chloride for a short time at 35–40°. Subsequent treatment with 0.5*N* hydrochloric acid gave rise to some of the corresponding hydroxyfurancarboxylic acid, XXXVIII, which undoubtedly exists in equilibrium with the tautomeric keto form, XXXIX. Thus, while the solution gives an intense red color with ferric chloride, a degradation reaction takes place with aqueous barium hydroxide which results in the formation of acetoin and oxalic acid. This reaction is readily explainable on the basis of structure XXXIX which, as a vinylog of a lactone, should be susceptible to hydrolytic cleavage. On the basis of this hypothesis, the β-diketone, XL, is proposed as an intermediate which, in accordance with the behavior of such types in basic medium, is further cleaved to the observed degradation products. It is interesting to point out that XXXVIII ⇌ XXXIX gave positive iodoform and Fehling's tests, results which are consistent with the alkali-instability just mentioned. That is, decomposition to acetoin explains both tests. The carboxyl group is readily removed

[44] Votoček and Malachta, *Collection Czechoslov. Chem. Communications*, **1**, 449 (1929); *C. A.*, **24**, 344 (1930).

[45] Votoček and Malachta, *Collection Czechoslov. Chem. Communications*, **4**, 87 (1932); *C. A.*, **26**, 3234 (1932).

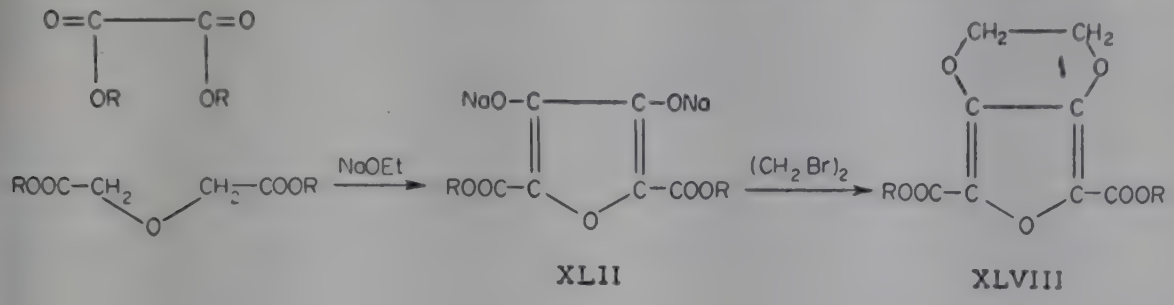


by application of heat, giving rise to two products, one of which analyzed correctly for the expected 2-methyl-3-furanol (b.p. 63–64° at 12 mm.). As before, the evidence points to the existence of this β-furanol in equilibrium (XLI) with its keto tautomer, the latter predominating. Thus, Zerewitinoff determination of active hydrogen gave only about one-third of the theoretical amount of methane. With barium hydroxide, the product was cleaved to acetoin; presumably formic acid was the other degradation product.

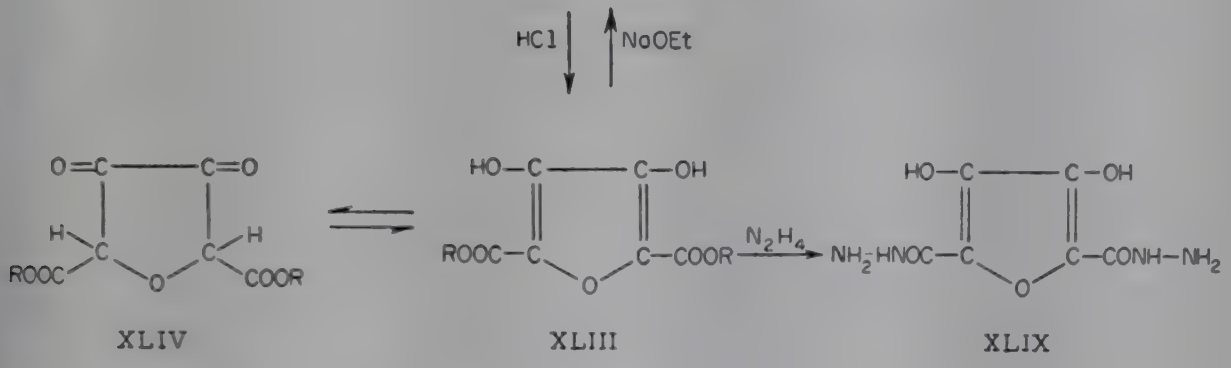
In contrast to these findings is the reported behavior of alkyl 3,4-dihydroxy-2,5-furandicarboxylate which was obtained by condensation of oxalic ester with diglycolic ester under the influence of sodium ethoxide. While Johnson and Johns[46] originally assigned the keto configuration, XLIV, subsequent work strongly indicates the enolic structure, XLIII. For example, Hinsberg[47] observed the product to give an intense blue-violet color with ferric chloride. More important, Hoehn[48] reports successful alkylation with methyl sulfate to yield the mono- and dimethoxy derivatives, XLV and XLVI, respectively. Additionally, Hoehn was able to acylate the remaining hydroxyl group of XLV, and in this way he obtained mixed methoxy-acyloxy derivatives, XLVII. XLIII also forms a stable disodium salt, XLII[46] from which Iyer and Guha[49, 50] have recently prepared a number

[46] Johnson and Johns, *Am. Chem. J.*, **36**, 290 (1906).
[47] Hinsberg, *Ber.*, **45**, 2413 (1912).
[48] Hoehn, *Iowa State Coll. J. Sci.*, **11**, 66 (1936).
[49] Iyer and Guha, *J. Indian Inst. Sci.*, **21**, A, 115 (1938); *C. A.*, **33**, 2134 (1939).
[50] Iyer and Guha, *J. Indian Inst. Sci.*, **23**, A, 159 (1941); *C. A.*, **36**, 3157 (1942).

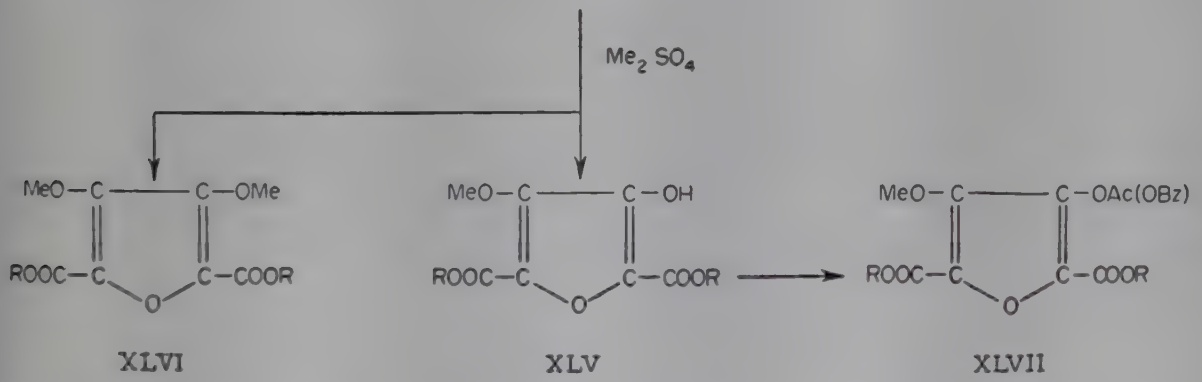
of interesting derivatives, including 3,4-(2,5-dicarbalkoxy)furodioxan, XLVIII, by the action of ethylene dibromide. No keto derivatives have



XLII XLVIII

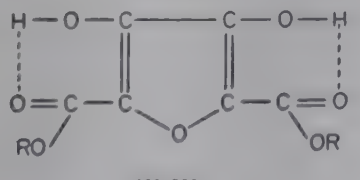


XLIV XLIII XLIX



XLVI XLV XLVII

been reported[48]; reaction of XLIII with hydrazine gives rise to the dihydrazide, XLIX.[51] Possibly this apparently well-developed tendency for XLIII to react in the enolic form is due to stabilization of this form by chelate hydrogen bonding as indicated below. No similar possibility existed with the other β-furanols which have been discussed, and which appear to exist largely in the tautomeric keto configuration.

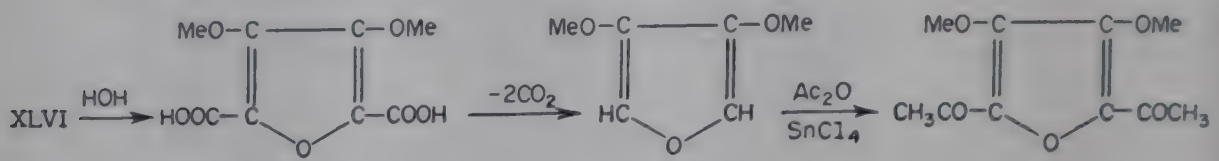


XLIII

Alkaline hydrolysis of XLVI produces the corresponding dicarboxylic

[51] Darapsky and Stauber, *J. prakt. Chem.*, **146**, 209 (1936).

acid, L, which was decarboxylated to 3,4-dimethoxyfuran, LI.[48] Acylation of LI with acetic anhydride in the presence of stannic chloride introduced two acetyl groups to form 2,5-diacetyl-3,4-dimethoxyfuran, LII, as shown by regeneration of L on subsequent oxidation. These and the other known derivatives of 3,4-furandiol are described below.



L LI LII

Derivatives of 3,4-furandiol:

3,4-Dimethoxyfuran: LI; b.p. 94–96° (18 mm.); d_4^{25} 1.1316; n_D^{25} 1.4650. Forms maleic anhydride adduct, m.p. 92–94°. Mercuration gives rise to 3,4-dimethoxyfuranbis-2,5-mercuric chloride, m.p. 208° (dec.).[48]

2,5-Diacetyl-3,4-dimethoxyfuran: LII; b.p. 160° (18 mm.); n_D^{25} 1.5187.[48]

3,4-Dimethoxy-2-furoic acid: m.p. 170–171°. **Methyl ester,** m.p. 54–55°.[48]

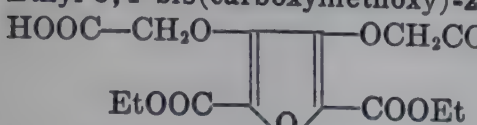
3-Hydroxy-4-methoxy-2-furoic acid: Unknown. **Methyl ester,** m.p. 100–101°.[48]

2,5-Dicarboxy-3,4-furandiol: Unknown. **Dihydrazide** (XLIX), not completely melted at 260°; **diazide,** explodes at 148–149°; **diurethan,** m.p. 147°.[51] For derivatives with sulfanilamide, see Jain, Iyer and Guha.[52, 53] **Esters:** dimethyl (XLIII, R = CH_3), m.p. 220°[47]; diethyl (XLIII, R = C_2H_5), m.p. 186, 189, 190°.[48, 46, 53a]

3,4-Dimethoxy-2,5-furandicarboxylic acid: XLVI (R = H), m.p. 243–245° (dec.). **Dimethyl ester** (XLVI, R = CH_3), m.p. 89.5–90°.[48]

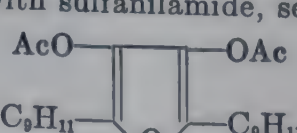
3-Hydroxy-4-methoxy-2,5-furandicarboxylic acid: Unknown. **Dimethyl ester** (XLV, R = CH_3), m.p. 150–151°. Acylation of the ester gave rise to the corresponding 3-acetoxy (m.p. 108°) and 3-benzoxy (m.p. 117–118°) derivatives, XLVII.[48]

Ethyl 3,4-bis(carboxymethoxy)-2,5-furandicarboxylate:



; m.p. ($+H_2O$) 221–225° (dec.). The corresponding **tetraethyl ester,** m.p. 65°, was obtained by the action of bromoacetic ester on the disodium salt, XLII, of XLIII (R = C_2H_5).[50]

3,4-(2,5-Dicarboxy)furodioxan: XLVIII (R = H); m.p. 316°. The product, which strongly resists decarboxylation was derived from the corresponding **diethyl ester,** m.p. 174–175°.[49] For condensation with sulfanilamide, see Jain, Iyer and Guha.[52, 53]



2,5-Dimesityl-3,4-diacetoxyfuran: ; m.p. 154.5–155°.[26]

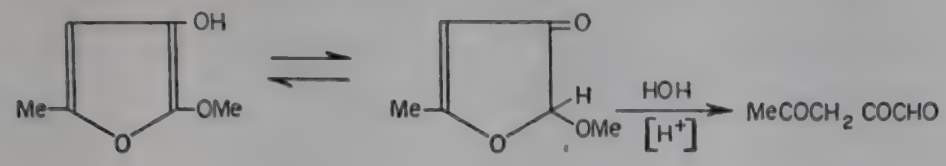
2,5-Dimesityl-3,4-dipropionyloxyfuran: m.p. 72–72.5°.[26]

Miscellaneous

2-Methoxy-5-methyl-3-furanol: LIII; b.p. 75–80° (3 mm.); m.p. 46–47.5°; obtained in 71 per cent yield by heating $MeOCH_2COCHClCOMe$ with acetic acid and

[52] Jain, Iyer and Guha, *Science and Culture*, **11**, 270 (1945); *C. A.*, **40**, 2125 (1946).
[53] Jain, Iyer and Guha, *J. Indian Chem. Soc.*, **24**, 177 (1947); *C. A.*, **43**, 2597 (1949).
[53a] Eastman and Wagner, *J. Am. Chem. Soc.*, **71**, 4089 (1949).

potassium acetate. Appears to exist in the two tautomeric forms shown below, and is cleaved readily by dilute acids to form 2,4-dioxopentanal, LIV.[54])



LIII LIV

2-Phenoxy-5-methyl-3-furanol: b.p. 143° (1–2 mm.); m.p. 63–64°.[54]
2-Acetyl-4-chloro-5-methyl-3-furanol: m.p. 83–84°. Reported as the product obtained by heating 3,5-dichloro-2,6-dimethylpyrone with barium hydroxide.[55]
2,5-Diphenyl-4-chloro-3-furyl acetate: m.p. 119°; by the action of acetic anhydride and sulfuric acid on either *cis*-1,4-diphenyl-2-chloro-2-buten-1,4-dione, or 1,4-diphenyl-1-chloro-2-hydroxy-1,4-butandione.[56]

Furylamines and Their Derivatives

Considerable difficulty has been experienced in preparing furan compounds possessing a free amine group on the nucleus. This is particularly true of the simple furylamines, which are very unstable, especially under hydrolytic conditions which invariably bring about deaminative degradation.

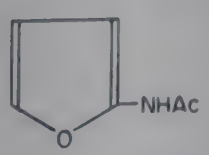
For a long time, the only known aminofurans were types with stabilizing nuclear substituents such as carboxyl, carbalkoxyl and nitro groups. In recent years, however, two homologs of 3-furylamine have been successfully prepared and while 3-furylamine itself and the isomeric 2-furylamine have thus far defied isolation, they are known in the form of N-acyl derivatives (see Table 2).

Simple Furylamines and Their Homologs

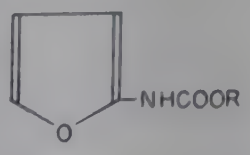
The early attempts to synthesize free amino derivatives of furan and its homologs were uniformly unsuccessful. Thus, while it was possible to isolate acylamino derivatives, attempted hydrolysis to the free amine always resulted in cleavage of the C-N linkages and liberation of ammonia. This was the experience of Marquis[57] (see also [58]) with N-2-furylacetamide, I, and of Freundler,[59] and Curtius and Leimbach[60] (see also [61, 62]) with 2-furyl-

[54] Henecka, Chem. *Ber.*, **82**, 32 (1949).
[55] Morgan and Porter, *J. Chem. Soc.*, **125**, 1269 (1924).
[56] Lutz, Stuart, Wilder and Connor, *J. Am. Chem. Soc.*, **59**, 2314 (1937).
[57] Marquis, *Ann. chim. phys.* (*8*), **4**, 196 (1905).
[58] Singleton and Edwards, *J. Am. Chem. Soc.*, **60**, 540 (1938).
[59] Freundler, *Bull. soc. chim.* (*3*), **17**, 419 (1897).
[60] Curtius and Leimbach, *J. prakt. Chem.*, **65**, 20 (1902).
[61] Marquis, *Compt. rend.*, **134**, 288 (1902).
[62] Pickard and Neville, *J. Chem. Soc.*, **79**, 847 (1901).

carbamic ester,[h] II, on either acidic or alkaline hydrolysis. Other synthetic



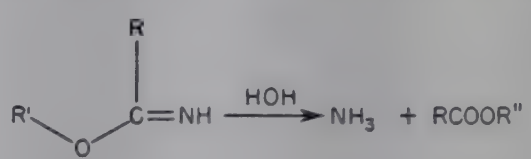
I



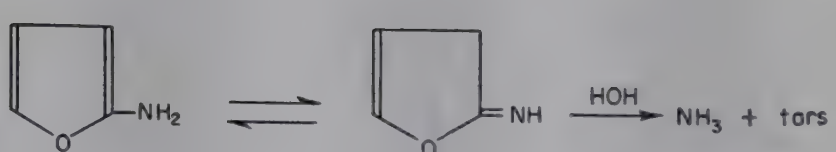
II

approaches which have failed include (1) Hofmann degradation of 2-furamide,[59, 63] (2) reduction of 2-nitrofuran,[57] (3) Beckmann rearrangement of phenyl 2-furyl ketoxime[57] (see also [64]), and (4) rearrangement of furohydroxamic acid.[64a]

This hydrolytic deamination is reminiscent of the behavior of imido esters, III, and suggests that 2-furylamine, IV, exists largely in the tautomeric form, V. To Stevenson and Johnson[65] it seemed evident that isolation



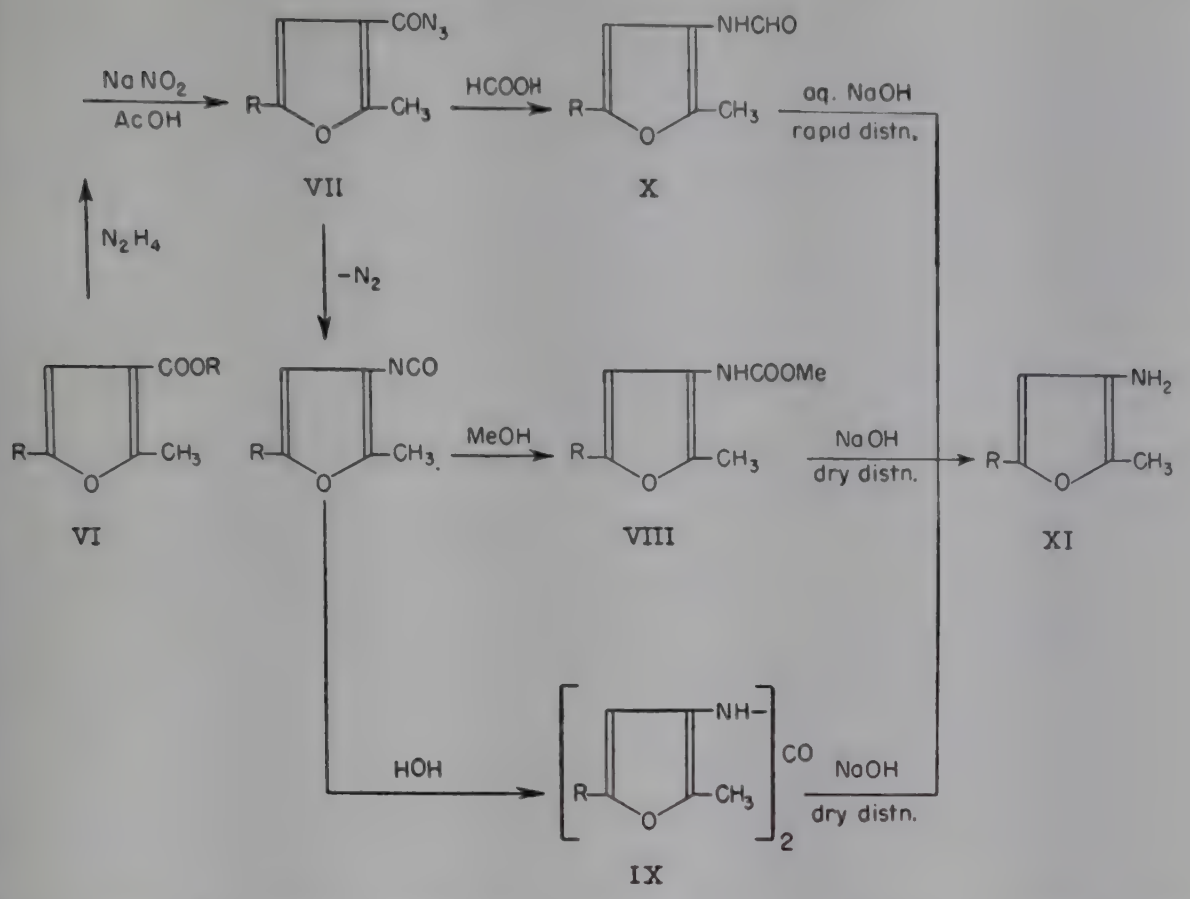
III



IV V

of a simple furylamine from furyl isocyanate or other acylamino derivative would depend on devising a special procedure to minimize contact with aqueous hydrolytic agents. They further reasoned that 3-furylamines would be somewhat more stable than the 2-isomers, and therefore selected derivatives of the former types for their studies. Starting with 2-methyl-3-furoic ester, VI (R = H), and 2,5-dimethyl-3-furoic ester (VI, R = CH_3), they prepared the corresponding methyl carbamates, VIII, and *sym*-ureas, IX (see also [66]), and from these (R = H), after several unsuccessful attempts, they were able to isolate 2-methyl-3-furylamine (XI, R = H) in an impure state by dry distillation with solid sodium hydroxide. Further work, however, disclosed a better method; a rapid, alkaline hydrolysis of the formamido

[63] Saunders, *Am. Chem. J.*, **15**, 130 (1893).
[64] Vargha, Ramonczai and Bite, *J. Am. Chem. Soc.*, **70**, 371 (1948).
[64a] Jones and Hurd, *J. Am. Chem. Soc.*, **43**, 2422 (1921).
[65] Stevenson and Johnson, *J. Am. Chem. Soc.*, **59**, 2525 (1937).
[66] Blomquist and Stevenson, *J. Am. Chem. Soc.*, **56**, 146 (1934).



derivatives, X, under special conditions produced the free amines in approximately 80 per cent yield. X was obtained by decomposition of the corresponding azide, VII, in the presence of glacial formic acid.

2-Methyl-3-furylamine (b.p. 51–52° at 4 mm.), and 2,5-dimethyl-3-furylamine (b.p. 55–56° at 4 mm.) are water-white liquids which, in odor, resemble dibutylamine and piperidine. They discolor rapidly on exposure to air, and give a strong carbylamine reaction. Benzoylation gives rise to the benzamido derivatives, identical to those obtained by the action of phenylmagnesium bromide on the appropriate isocyanates. With benzaldehyde, 2,5-dimethyl-3-furylamine, XII, forms an addition compound (XIV or XV) which resists dehydration to the expected Schiff's base. To account for this reaction, Stevenson and Johnson[65] postulate that XII exists in tautomeric equilibrium with the ketimine structure, XIII, the latter predominating. Supporting this view is the cleavage of the amine with aqueous alkali to acetic acid, acetoin and ammonia. These are the products to be expected

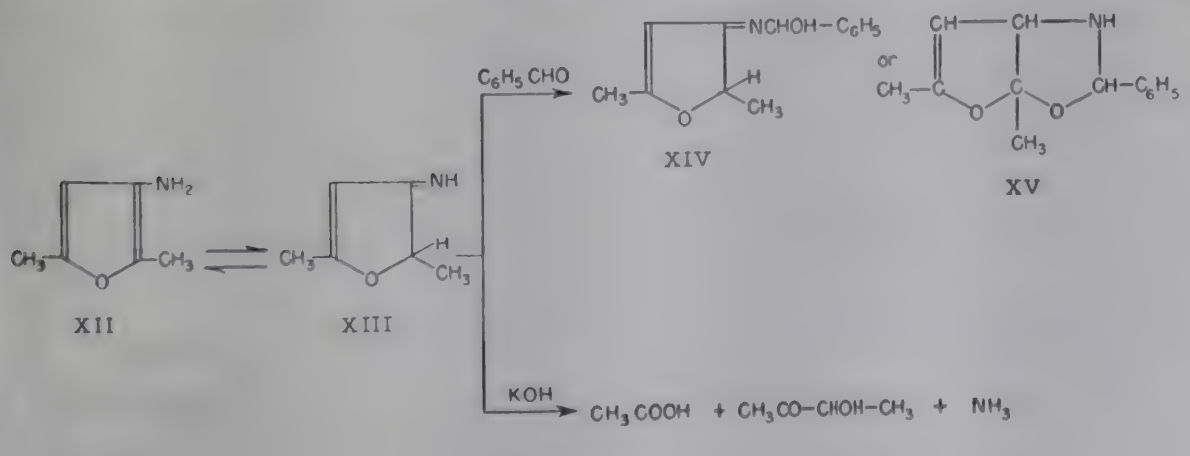
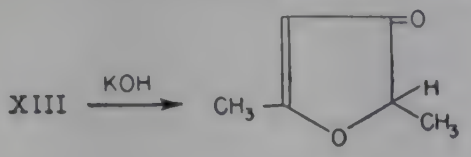


TABLE 2. DERIVATIVES OF 2- AND 3-FURYLAMINES AND THEIR HOMOLOGS

Derivative	Physical constants		Ref.
	b.p. (°C.)	m.p. (°C.)	
Isocyanates			
2-Furyl	110.5–111 (740 mm.)	—	65, 58
5-Methyl-2-furyl	53–54 (35 mm.)	—	66
5-Bromo-2-furyl	75 (35 mm.)	—	66
3-Furyl	not isolated		67
2-Methyl-3-furyl	42 (15 mm.)	—	66
2,4-Dimethyl-3-furyl	74–75 (31 mm.)	—	66
2,5-Dimethyl-3-furyl	68 (20 mm.)	—	66
N-acyl derivatives			
N-2-furylformamide	—	—	65
N-2-furylacetamide	—	112	68, 57, 69
N-2-furylpropionamide	134 (12 mm.)	80.5–81	58
N-2-furylbenzamide	—	124.5	58
N-(5-methyl-2-furyl)benzamide	—	75–80	66
N-3-furylbenzamide	—	142	67
N-(2-methyl-3-furyl)formamide	138–140 (8 mm.)	65.5–67	65
N-(2-methyl-3-furyl)acetamide	—	148	67
N-(2-methyl-3-furyl)benzamide	—	135, 137.8–138	67, 66, 65
N-(2,4-dimethyl-3-furyl)benzamide	—	169–170	66
N-(2,5-dimethyl-3-furyl)formamide	152–154 (11 mm.)	80.5–81.5	65
N-(2,5-dimethyl-3-furyl)benzamide	—	152–152.4	65
Furylcarbamic esters			
Methyl 2-furylcarbamate	115–120 (18 mm.)	135	59, 58, 60
Ethyl 2-furylcarbamate	133 (24 mm.)	—	59, 60, 57, 70
3-Piperidinopropylene bis(2-furylcarbamate)	—	—	71
Methyl (5-methyl-2-furyl)-carbamate	—	64–66	66
Methyl (2-methyl-3-furyl)-carbamate	128 (14 mm.)	—	66; see also 65
Methyl (2,4-dimethyl-3-furyl)carbamate	—	95–96	66
Methyl (2,5-dimethyl-3-furyl)carbamate	107 (2.5 mm.)	—	66
***sym.*-Difurylureas**			
Di-2-furylurea	—	190 (dec.), 220 (dec.)	58, 60; see also 65
Bis(5-methyl-2-furyl)urea	—	182	66
Bis(2-methyl-3-furyl)urea	—	227, 226	66, 67; see also 65
Bis(2,4-dimethyl-3-furyl)urea	—	285	66
Bis(2,5-dimethyl-3-furyl)urea	—	247	66

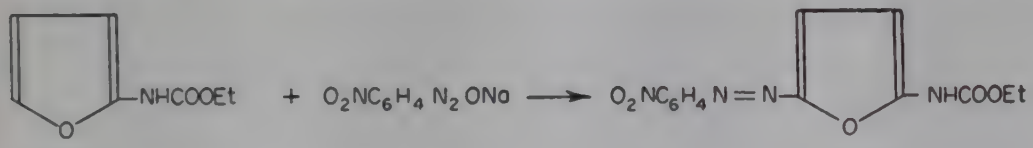
if the amine reacts in the form XIII, which is a vinylog of an imido ester; the reaction is closely related to the degradation of certain β-furanols (see p. 179), and it is possible that a furanol, in the tautomeric form, XVI, is formed as an intermediate. When heated with dilute sulfuric acid, 2-methyl-



XVI

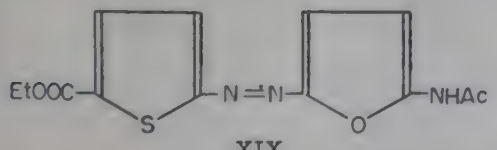
β-furylamine decomposes with nearly quantitative elimination of ammonia,[65] a result which likewise favors the ketimine or imido ester (vinylog) structure for this amine.

Attempted diazotization of these β-furylamines reveals certain abnormalities. For example, while the diazo solutions give rise to crystalline dyes with alkaline β-naphthol, they do not react normally in experiments designed to replace the diazo group by hydrogen and by the cyano group[66] (see also [72]). Coupling of the amines with diazonium salts has not been reported, but the reaction has been carried out with ethyl 2-furylcarbamate, XVII, and with N-2-furylacetamide. As in the thiophene series, acylation of the amino group does not destroy the power to couple. Thus, XVII and sodium *p*-nitrobenzenediazotate react to form ethyl 5-(*p*-nitrophenylazo)-2-furylcarbamate, XVIII, a yellow dye which melts, with decomposition, at 195°.[70] Similarly, N-furylacetamide couples with diazo

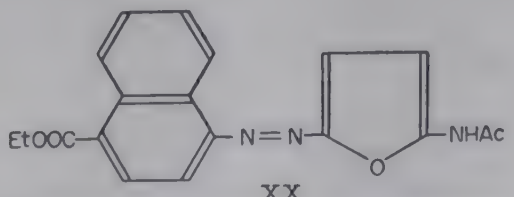


XVII XVIII

solutions derived from ethyl 5-amino-2-thiophenecarboxylate and ethyl 4-amino-1-naphthoate with formation of ethyl 5-(5-acetamido-2-furylazo)-2-thiophenecarboxylate, XIX (m.p. 191–192° (dec.)) and ethyl 4-(5-acetamido-2-furylazo)-1-naphthoate, XX (m.p. 124–125°, (after sintering)), respectively.[69]



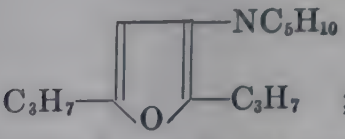
XIX



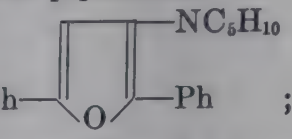
XX

[67] Burtner, *J. Am. Chem. Soc.*, **56**, 666 (1934).
[68] Marquis, *Compt. rend.*, **136**, 1454 (1903).
[69] Dann, *Chem. Ber.*, **82**, 72 (1949).
[70] Hurd and Priestley, *J. Am. Chem. Soc.*, **69**, 859 (1947).
[71] Welvart, *Bull. soc. chim. France*, **1949**, 332.
[72] Gilman and Wright, *Rec. trav. chim.*, **53**, 13 (1934).

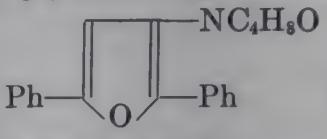
Miscellaneous:



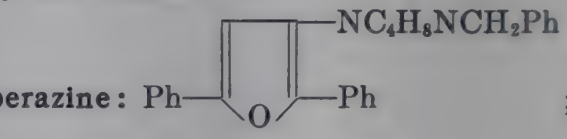
N-(2,5-dipropyl-3-furyl)piperidine: C_3H_7—(furan)—C_3H_7, NC_5H_{10} ; b.p. 83° (0.15 mm.) 110° (1 mm.); n_D^{17} 1.4909; **HCl salt,** m.p. 145.5–146° (dec.). Prepared by condensation of C_3H_7—CHOH—C≡C—COC_3H_7 with piperidine.[73]



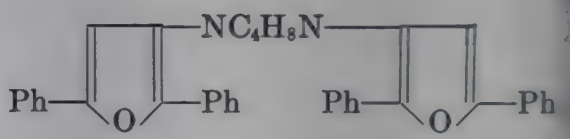
N-(2,5-diphenyl-3-furyl)piperidine: Ph—(furan)—Ph, NC_5H_{10} ; m.p. 102.5–103.5°; by cyclodehydration of 1,4-diphenyl-2-N-piperidine-1,4-butandione.[74]



N-(2,5-diphenyl-3-furyl)morpholine: Ph—(furan)—Ph, NC_4H_8O ; m.p. 113–114°.[74] For attempted chloroethylation, see Bailey and Hakki.[75]



N-(2,5-diphenyl-3-furyl)-N′-benzylpiperazine: Ph—(furan)—Ph, $NC_4H_8NCH_2Ph$; m.p. 70–72°.[74]



1,4-Bis(2,5-diphenyl-3-furyl)piperazine: Ph—(furan)—Ph, Ph—(furan)—Ph, NC_4H_8N m.p. 266–267°.[74]

Aminofuroic Acids

Marquis[68, 57] was successful in preparing ethyl 5-amino-2-furoate, I, by reduction of the corresponding nitro ester with aluminum amalgam. Later[76] (see also [17, 77]) this reduction was accomplished more conveniently by catalytic hydrogenation over platinum. Marquis had hoped to convert I into the free amino acid, and thence, by decarboxylation, to the elusive 2-furylamine.[1] Saponification could not be carried out, however, without complete destruction. On the other hand, protection of the amino group by acetylation permitted saponification (5 per cent K_2CO_3 at reflux) of the resulting acetamido ester, to 5-acetamido-2-furoic acid, II, which gave rise to N-2-furylacetamide, III, following decarboxylation. As indicated in the previous section, however, all attempts to hydrolyze III to the free amine have been fruitless.

[1] Marquis erroneously assigned the nitro group, and therefore the resulting amino group to a β-nuclear carbon atom.

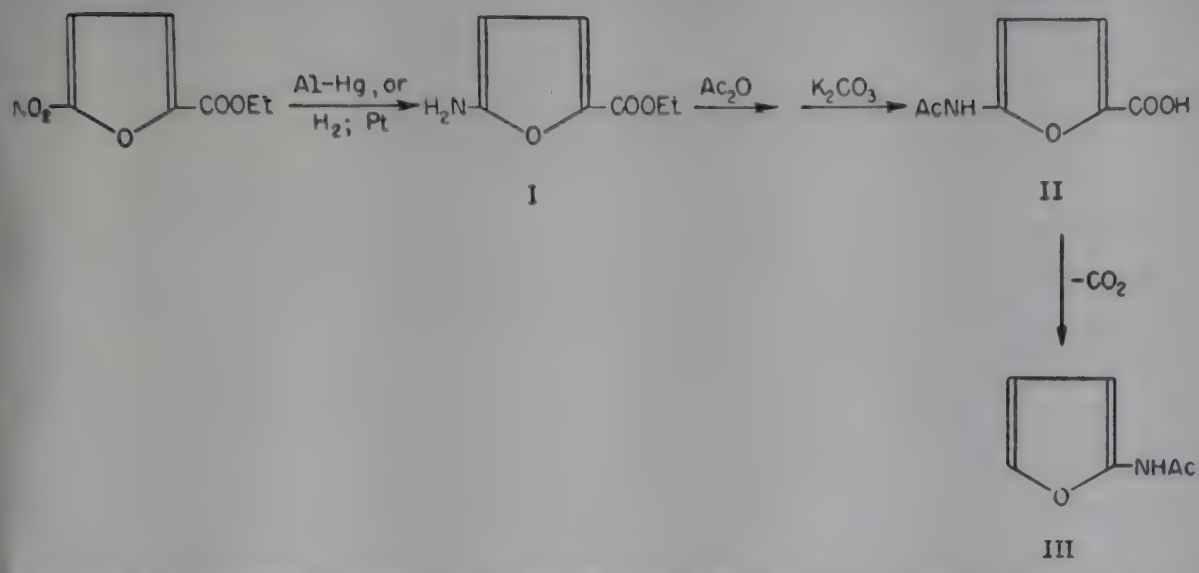
[73] Bowden, Braude, Jones and Weedon, *J. Chem. Soc.*, **1946**, 45.

[74] Lutz, Bailey and Shearer, *J. Am. Chem. Soc.*, **68**, 2224 (1946).

[75] Bailey and Hakki, *J. Am. Chem. Soc.*, **71**, 2886 (1949).

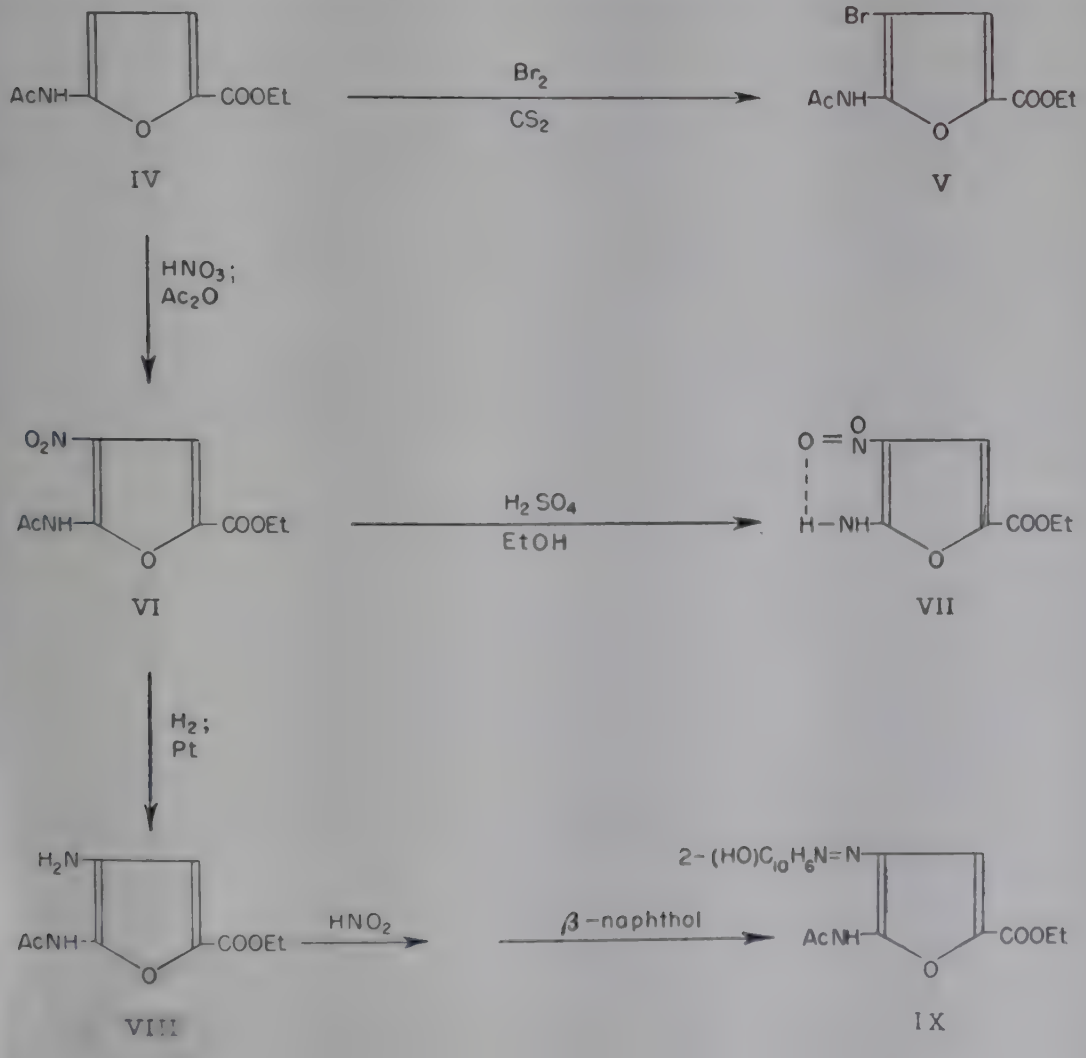
[76] Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931).

[77] Dann, *Ber.*, **76**, 419 (1943).

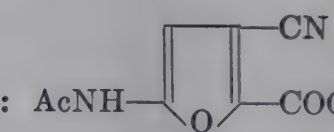


5-Amino-2-furoic ethyl ester: m.p. 95°.[68, 57] The β-diethylaminoethyl ester is known as the hydrochloride, m.p. 154–157°.[77] For the anesthetic properties of these esters, the furan analogs of anesthesin and novocaine, respectively, see Dann[77] (see also [78]). The **5-acetamido acid** decomposes at 285°[68, 57]; **ethyl ester,** m.p. 177.5°[68, 57] (see also [76]). **Ethyl 5-benzamido-2-furoate,** m.p. 99–100°[68, 57]

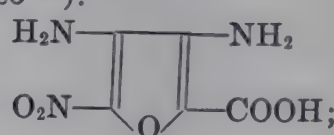
The acetamido ester, IV, is converted into 4-bromo-5-acetamido-2-furoic ester, V (m.p. 112°) by the action of bromine in carbon disulfide.[76] The introduction of a nitro group has also been accomplished with formation of VI (m.p. 138°).[76, 17] Refluxing VI with sulfuric acid in alcohol gives rise to ethyl 4-nitro-5-amino-2-furoate, VII (m.p. 150, 153°) in excellent yield[72] (see also [17]); the stability of VII, its resistance to deamination and destruction under these conditions, is perhaps attributable to chelate hydrogen bonding as indicated below. Catalytic reduction of VI produces the



amino acetamido ester, VIII (m.p. 160.5°), which following diazotization may be coupled with β-naphthol to obtain IX (m.p. 223.5–224.5° (dec.)).[71] When the diazo solution is treated with copper and hydrobromic acid however, IV is obtained instead of V, the expected Gattermann product. Attempted diazotization of VIII in sulfuric acid resulted in copious evolution of nitrogen, but the reaction mixture gave a positive diazo test and was treated with copper and hydrocyanic acid in the hope of obtaining the appropriate cyano acetamido ester. Instead, the sole product which was isolated gave the correct analysis for ethyl 4-hydroxy-5-acetamido-2-furoate (m.p. 143–144°).[72] VII was recovered unchanged from a number of different methods of diazotization. I,[69] and its picrate[72] are both resistant to the action of nitrous acid.



3-Cyano-5-acetamido-2-furoic acid: AcNH—(C=C)—COOH; m.p. 249° (dec.); **ethyl ester,** m.p. 177°. The corresponding **5-benzamido acid,** m.p. 256° (dec.); **ethyl ester,** m.p. 168–169°[79] (see also [72]).

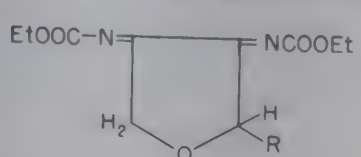


3,4-Diamino-5-nitro-2-furoic acid: O_2N—(C=C)—COOH; chars above 300°.[80]

3,4-Furandiamine and Related Types

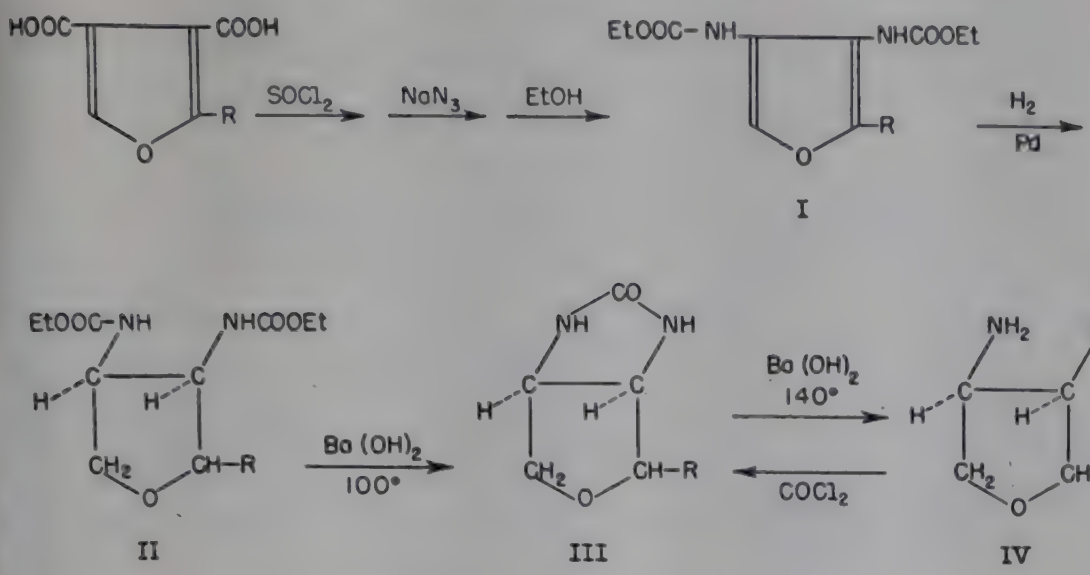
With the two exceptions noted above (this page), no furandiamines had been reported prior to the recent studies of Hofmann and Bridgwater[81] (see also [82]). Using a modified Curtius degradation, these investigators converted several 2-substituted 3,4-furandicarboxylic acids into urethans (i.e., I) of the corresponding 3,4-furandiamines. Hydrogenation of I at room temperature[m] in acetic acid over a palladium-on-barium sulfate catalyst

[m] Hofmann[83] calls attention to the ease of hydrogenation of furans of type I, and contrasts it with the behavior of the corresponding 3,4-furandicarboxylic acids which are very resistant to catalytic hydrogenation. He attributes the former to the existence of I in tautomeric equilibrium with the imino form, Ia (see also p. 184).



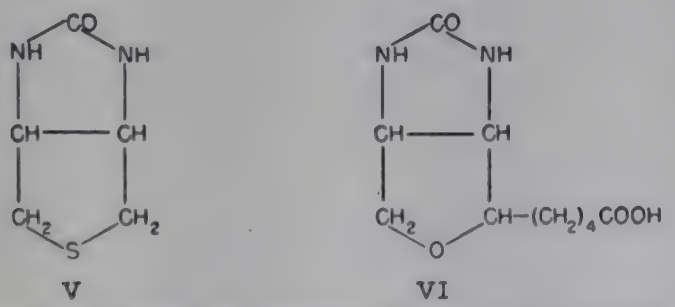
Io

[78] Dann and Möller, *Chem. Ber.*, **80**, 21 (1947).
[79] Dieckmann, *Ber.*, **44**, 981 (1911).
[80] Traube and Lazar, *Ber.*, **46**, 3438 (1913).
[81] Hofmann and Bridgwater, *J. Am. Chem. Soc.*, **67**, 738 (1945).
[82] Stork, *J. Am. Chem. Soc.*, **67**, 884 (1945).
[83] Hofmann, *J. Am. Chem. Soc.*, **67**, 1459 (1945).



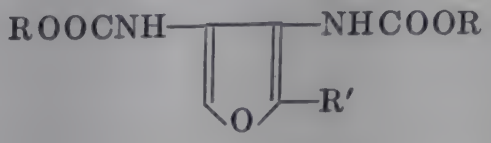
gives rise to a mixture of products from which ethyl 2-R-tetrahydrofuran-*cis*-3,4-dicarbamate, II, may be isolated.[83, 84, 85, 86, 87] Mild hydrolysis of II with dilute barium hydroxide fails to give the expected tetrahydrofurandiamine, IV; instead, there is formed the bicyclic imidazole derivative, III, which can be cleaved with strong base at 140° to obtain IV[84] (see also [83]).

The ring system of III is closely related to the biotin nucleus, V, and Hofmann and his associates[83, 88, 89] synthesized a number of these O-analogs for biological investigation. For example, III [R = $(CH_2)_4CH_2OH$] was synthesized and oxidized with alkaline potassium permanganate to obtain *dl*-desthiooxybiotin, VI, the oxygen analog of biotin. This replacement of sulfur by oxygen does not alter the biological activity significantly.[83, 88]



[84] Hofmann and Bridgwater, *J. Am. Chem. Soc.*, **67**, 1165 (1945).
[85] Hofmann (to Ciba Pharmaceutical Products Inc.), U. S. Pat. 2,506,594 (1950).
[86] Hofmann (to Ciba Pharmaceutical Products Inc.), U. S. Pat. 2,520,404 (1950).
[87] Hofmann (to Ciba Pharmaceutical Products Inc.), U. S. Pat. 2,453,627 (1948); *C. A.*, **43**, 1441 (1949).
[88] Hofmann, Chen, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **69**, 191 (1947).
[89] Hofmann, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **69**, 1550 (1947); **71**, 1253 (1949).

TABLE 3. URETHAN DERIVATIVES OF 3,4-FURANDIAMINES



R	R′	M.p. (°C.)	Ref.
C_2H_5	H	166–167	82
C_2H_5	CH_3	105–107	81, 87, 9
$C_6H_5CH_2$	CH_3	122–124	81
C_6H_5	CH_3	190–195	90
C_2H_5	$(CH_2)_2CH_2OH$	74–77	88
C_2H_5	$(CH_2)_3CH_2OH$	77–79	85, 89
C_2H_5	$(CH_2)_4CH_2OH$	79–81, 80–82 (acetate, 56–58)	83, 90, 8
C_2H_5	$(CH_2)_4COOH$	— (piperidide, 89–91)	81, 90
$C_6H_5CH_2$	$(CH_2)_4COOH$	— (piperidide, 129–131)	81

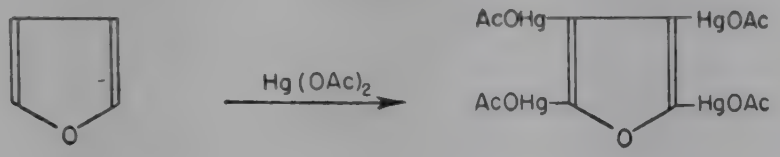
[90] Hofmann, Brit. Pat. 615,908 (1949); *C. A.*, **43**, 5805 (1949).

Chapter 6

FURAN METALLIC COMPOUNDS

Furan Mercurials

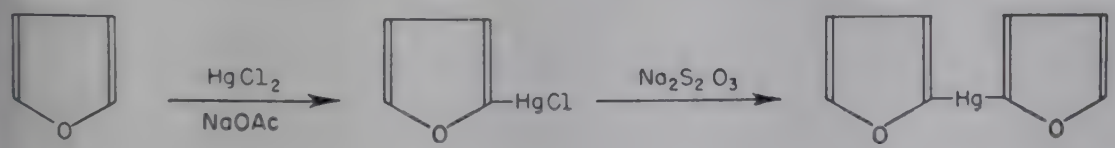
Furylmercuric chlorides and acetates comprise the bulk of the known furan derivatives of mercury. Ciusa and Grilla[1] were the first to obtain clean-cut evidence for such compounds. From furan and aqueous mercuric acetate, they isolated 2,3,4,5-furantetrakis(mercuric acetate), I. Treat-



I

ment of furoic acid with mercuric acetate brought about decarboxylation and formation of the same mercurial. By the action of sodium chloride, I is converted into furantetrakis(mercuric chloride).

This work was greatly extended by Gilman and Wright,[2] who found that monosubstitution products are obtainable in 35–70 per cent yield when certain furan types are placed in reaction with an equimolecular quantity of mercuric chloride or acetate in the presence of sodium acetate. With an excess of mercury salt, polysubstitution products are obtained. Among other mercurials, these investigators prepared 2-furylmercuric chloride, II, and reported its conversion to di-2-furylmercury, III, by reduction with sodium thiosulfate. Coupling to III was also achieved by treating II with hydrazine hydrate, and with sodium iodide in acetone.

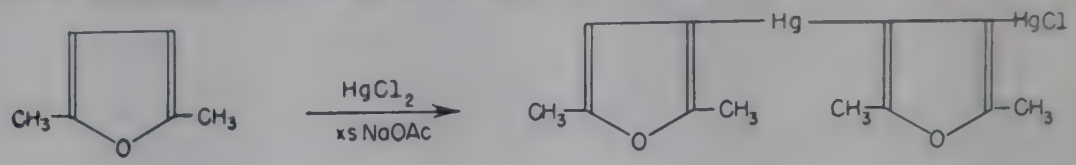


II III

The alpha nuclear positions are more reactive than the beta positions but, in general, the latter react quite readily when the former are occupied by irreplaceable groups. From 2,5-dimethylfuran, Hurd and Wilkinson[3] prepared 2,5-dimethyl-3-furylmercuric chloride, and also the corresponding

[1] Ciusa and Grilla, *Gazz. chim. ital.*, **57**, 323 (1927); *C. A.*, **21**, 2686 (1927).
[2] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).
[3] Hurd and Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

3,4-bis(mercuric chloride). It is interesting to note, however, that when the reaction with mercuric chloride was carried out in the presence of a relatively large amount of sodium acetate, a compound was obtained which analyzed correctly for 4-(2,5-dimethylfurylmercuri)-2,5-dimethyl-3-furylmercuric chloride, IV. The likelihood of this structure is supported by



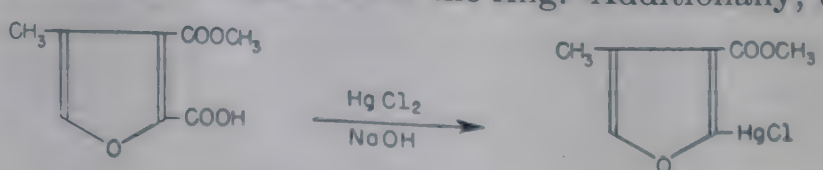
IV

conversion of the compound to 3,4-diiodo-2,5-dimethylfuran by iodination with iodine and potassium iodide.

Yet another effect of the concentration of sodium acetate has been observed in connection with the mercuration of 2-methylfuran with one equivalent of mercuric chloride. When the reaction is carried out in the presence of two equivalents of sodium acetate, an intermediate addition compound is obtained, the composition of which approximates that of a complex of methylfuran, basic mercuric chloride, and mercuric chloride. Refluxing in alcohol transforms the complex into 5-methyl-2-furylmercuric chloride, which is formed directly when the initial mercuration mixture contains four equivalents of sodium acetate.[2]

Furans mercurate more readily than their thiophene analogs. The only reported effect of substituent groups on ease of reaction concerns the failure of 2-nitrofuran and 2,5-diiodofuran to react with mercuric chloride, at least under moderate experimental conditions.[2] Forced conditions might have induced reaction. For example, although sodium 5-nitro-2-furoate fails to react even at reflux, it is transformed into 5-nitro-2-furylmercuric chloride when heated with aqueous mercuric chloride at 150–160° for one hour.[2]

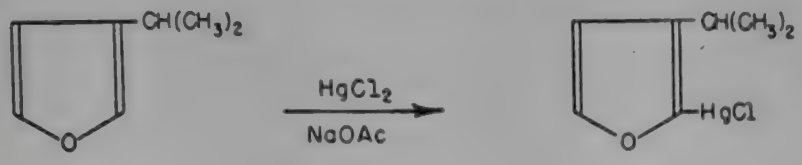
The replacement-decarboxylation reaction was studied at considerable length by Gilman and his students, who observed that replacement of the carboxyl group of 2-furoic acids by an incoming mercuric chloride radical takes place even more readily than direct substitution. For example, sodium 2,4-furandicarboxylate is readily transformed into 4-carboxy-2-furylmercuric chloride.[4] Again, mercuration of 3-carbomethoxy-4-methyl-2-furoic acid brings about replacement of the α-carboxyl to form V, rather than substitution at the open 5-position of the ring.[5] Additionally, the action of



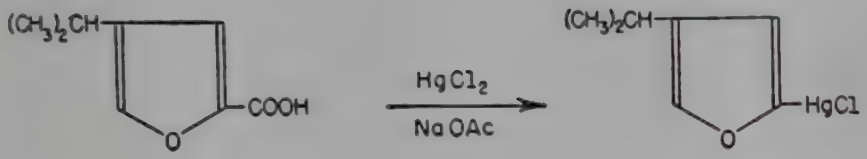
V

[4] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).
[5] Gilman and Burtner, *J. Am. Chem. Soc.*, **71**, 1213 (1949).

mercuric chloride on 3-isopropylfuran gives rise to 3-isopropyl-2-furylmercuric chloride, VI, whereas 4-isopropyl-2-furoic acid is converted into the

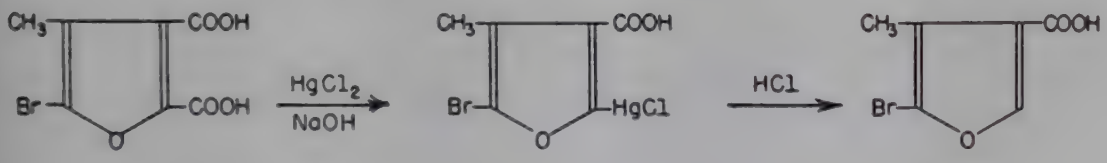


VI



VII

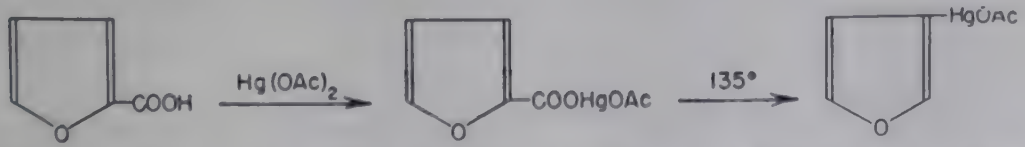
isomeric 4-isopropyl-2-furylmercuric chloride, VII.[6] Replacement-decarboxylation, however, is limited to α-nuclear carboxyl groups,[2] a circumstance which was employed to advantage by Gilman and Burtner[5] for the synthesis of 5-bromo-4-methyl-3-furoic acid, VIII. The reaction sequence offers a particularly mild and convenient method for decarboxylating 2-furoic acids,



VIII

the carbon-metal bond of the intermediate mercurial being subject to facile cleavage in acidic medium (see Table 2).

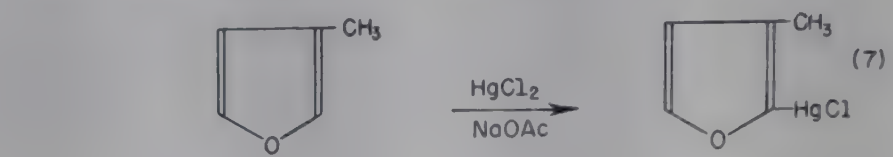
Surprisingly, none of the furoic acids appears to form insoluble mercuric furoates under the conditions of mercuration. On the other hand, the ready formation of a mixed mercuric salt from 2-furoic acid and aqueous mercuric acetate affords a satisfactory method of β-mercuration.[5] The mixed salt (acetoxymercury furoate) undergoes a complex rearrangement on heating to 135° to form 3-furylmercuric acetate, which may be converted into the corresponding chloride by treatment with aqueous chloride ion.



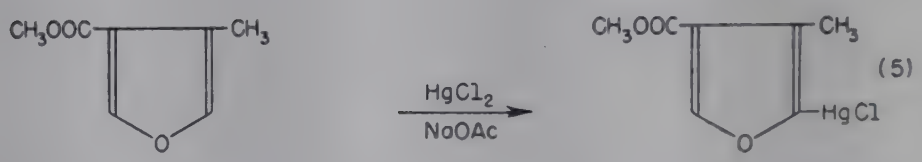
Comparatively little data are available with reference to the effect of resident groups on orientation, although it appears that substituents which orient ortho-para in the benzene series activate an unsubstituted position

[6] Gilman, Calloway and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).

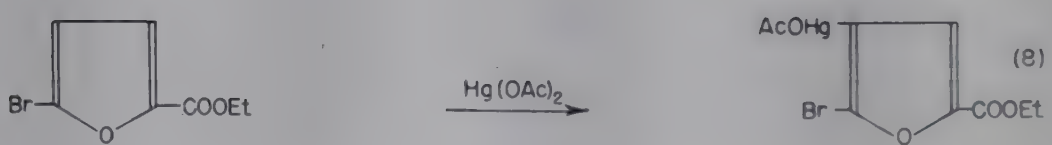
on the same side of the furan nucleus, and that meta directors deactivate these positions. On the other hand, the tendency for alpha substitution is so well developed that this takes precedence if an alpha position is available, either unoccupied, or with a carboxyl group. Illustrative are the equations which follow (see also VI and VII, above).



(7)



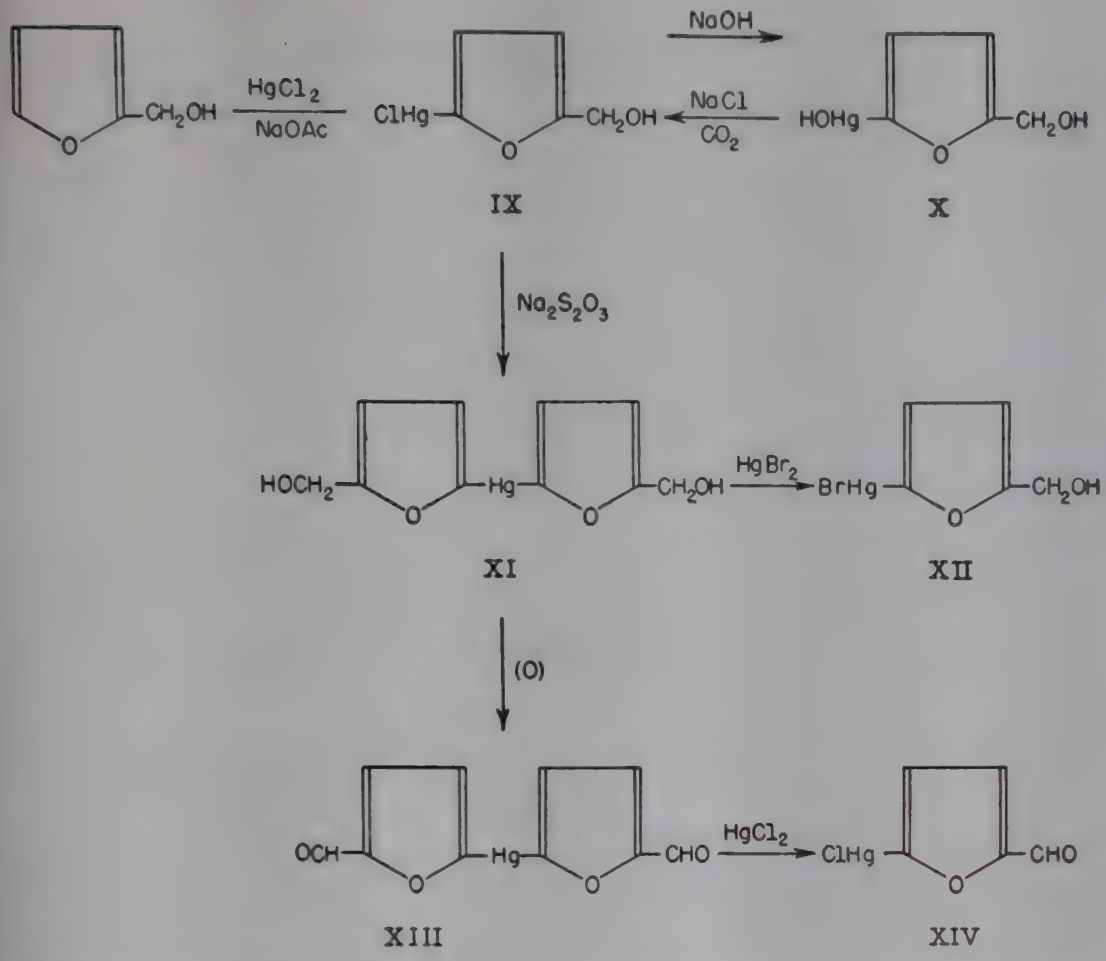
(5)



(8)

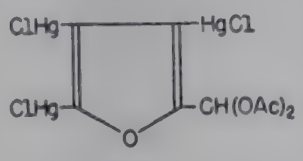
Marini-Bettolo and co-workers[9, 10, 11] obtained an indefinite compound from furfural and mercuric chloride. By electron diffraction, however, they were able to show that a C-Hg bond was present in the reaction product of furfuryl alcohol and mercuric chloride. Shortly thereafter, Wright and his students[12] isolated pure 5-hydroxymethyl-2-furylmercuric chloride, IX, from the latter reaction by employing a three-fold excess of furfuryl alcohol. With sodium hydroxide, IX gives rise to the corresponding mercuric hydroxide derivative, X, from which IX is regenerated by treating with carbon dioxide in aqueous sodium chloride. IX and acetic anhydride give the corresponding ester, 5-(acetoxymethyl)-2-furylmercuric chloride. Bis [(5-hydroxymethyl)-2-furyl]mercury, XI, is formed in approximately 60 per cent yield when IX is placed in reaction with aqueous sodium thiosulfate, or with diazomethane in methanol. With mercuric bromide XI is converted into 5-(hydroxymethyl)-2-furylmercuric bromide, XII. Oxidation of XI

[7] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 859 (1933).
[8] Beck and Hamilton, *J. Am. Chem. Soc.*, **60**, 620 (1938).
[9] Baroni and Marini-Bettolo, *Gazz. chim. ital.*, **70**, 670 (1940); *C. A.*, **35**, 5106 (1941).
[10] Marini-Bettolo and Paolini, *Gazz. chim. ital.*, **75**, 78 (1945); *C. A.*, **41**, 3444 (1947).
[11] Borzini and Marini-Bettolo, *Bol. staz. patol. vegetale*, **18**, 347 (1940); *C. A.*, **35**, 564 (1941).
[12] Chute, Orchard and Wright, *J. Org. Chem.*, **6**, 157 (1941).



with potassium permanganate results in the formation of bis(5-formyl-2-furyl)mercury, XIII, which is converted into 5-formyl-2-furylmercuric chloride, XIV, following treatment with mercuric chloride.[12] XIV has also been reported recently by direct mercuration of furfural.[13]

Related to XIV is 5-diacetoxymethyl-2,3,4-furantris(mercuric chloride), XV, which was obtained by the action of mercuric acetate on furfurylidene diacetate, and subsequent treatment of the resulting tris(mercuric acetate) derivative with sodium chloride.[14]



XV

The furan mercurials are readily cleaved by acids (Table 2). They react with bromine and iodine to form the corresponding halofuran (Table 3), frequently the best method for preparing the latter types. 2- and 3-Iodofuran,[2] for example, and 5-bromo- and 5-iodofurfuryl alcohol[12] have been synthesized in this way. In these cleavage reactions, it has been observed

[13] Irie and Wakayama, *Science Japan*, **18**, 328 (1948); *C. A.*, **45**, 4213 (1951).
[14] Scheibler, Jeschke and Beiser, *J. prakt. Chem.*, **136**, 232 (1933).

TABLE 1. FURAN MERCURIALS

Modes of Preparation:
A. Replacement of carboxyl group
B. Direct mercuration of corresponding furan
C. Reaction of corresponding mercuric acetate derivatives with chlori

Compound	M.p. (°C.)	Prepn.	R
2-Furylmercuric chloride	152, 152–153	B	2, 1 17
2-Furylmercuric hydroxide	dec. 101	—	16
2-Furylmercuric nitrate	dec. 168	—	18
3-Furylmercuric chloride	184.5	C	2
2,5-Furanbis(mercuric chloride)	—	B	2, 16
2,3,4,5-Furantetrakis(mercuric chloride)	dec. 235	C	1, 19
2,3,4,5-Furantetrakis(mercuric acetate)	dec. 226–228	B	1, 19
2,3,4,5-Furantetrakis(mercuric hydroxide)	—	—	1
3-Methyl-2-furylmercuric chloride	142	B	4, 7
5-Methyl-2-furylmercuric chloride	132, 134	A, B	2, 18
5-Ethyl-2-furylmercuric chloride	109	B	23
3-Isopropyl-2-furylmercuric chloride	90	B	24
4-Isopropyl-2-furylmercuric chloride	119–120	A	24
5-*n*-Propyl-2-furylmercuric chloride	99	B	25
5-Isopropyl-2-furylmercuric chloride	117–118	B	25
5-*n*-Butyl-2-furylmercuric chloride	79–80, 80–81	B	25, 2
5-Isobutyl-2-furylmercuric chloride	95–96	B	25
5-*s*-Butyl-2-furylmercuric chloride	88	B	25
5-*t*-Butyl-2-furylmercuric chloride	174–175°	B	26, 1
5-*n*-Pentyl-2-furylmercuric chloride	84–85	B	27
5-Benzyl-2-furylmercuric chloride	121	B	23
5-Furfuryl-2-furylmercuric chloride	149.5	B	2
5-(3-Phenylpropyl)-2-furylmercuric chloride	94–95	B	28
3,5-Dimethyl-2-furylmercuric chloride	112	B	29
2,5-Dimethyl-3-furylmercuric chloride	164	B	16, 2
2,5-Dimethyl-3,4-furanbis(mercuric chloride)	—	B	3
5-Chloro-2-furylmercuric chloride	181	A	30
3,4-Dichloro-2-furylmercuric chloride	171–172	A	31, 3
3,5-Dichloro-2-furylmercuric chloride	123–124	A	31
4,5-Dichloro-2-furylmercuric chloride	182–182.5	A	31
5-Bromo-2-furylmercuric chloride	177, 173	A, B	2, 32
5-Iodo-2-furylmercuric chloride	169, 173	A, B	2, 34
5-Methyl-3-iodo-2-furylmercuric chloride	193.5	B	2
5-Nitro-2-furylmercuric chloride	208	A	2, 17
3,4-Dimethoxy-2,5-furanbis(mercuric chloride)	208 (dec.)	B	35

TABLE 1—*Continued*

Compound	M.p. (°C.)	Prepn.	Ref.
roxymethyl-2-furylmercuric chloride	144.5–145.5	B	12
roxymethyl-2-furylmercuric bromide	139–140	—	12
roxymethyl-2-furylmercuric hydroxide	156–157 (impure)	—	12
oxymethyl-2-furylmercuric chloride	131–131.5	—	12
oxymethyl-2-furylmercuric bromide	108–109	—	12
anidomethyl-2-furylmercuric chloride	182–184	A	20
uanidomethyl-2-furylmercuric chlo-	186–187	A	20
yl-2-furylmercuric chloride	213–213	—	12, 13
etoxymethyl-2,3,4-furantris(mercuric ride	—	C	14
etoxymethyl-2,3,4-furantris(mercuric ate)	—	B	14
oxy-2-furylmercuric chloride	—	A	4
omethoxy-2-chloro-3-furylmercuric ride)	215–217	B	31
omethoxy-2-bromo-3-furylmercuric ride	238	C	8; see also 31
oethoxy-2-bromo-3-furylmercuric ride	162	C	8
omethoxy-2-bromo-3-furylmercuric ate	136–139	B	8
oethoxy-2-bromo-3-furylmercuric ate	138–139	B	8
omethoxy-3-methyl-2-furylmercuric ride	175	B	5
omethoxy-4-methyl-2-furylmercuric ride	141–142	A	5
methoxy-5-carbomethoxy-2-furylmer- chloride	112–113.5	B	35
yl-4-carboethoxy-2,3-furanbis(mer- chloride)	—	B	31
urylmercury	114; b.p. 156 (7 mm.)	—	2, 16
urylmercury	73; b.p. 152–153 (5.5 mm.)	—	2
ydroxymethyl-2-furyl)mercury	153–154	—	12
formyl-2-furyl)mercury	262–263 dioxime, 144–116	—	12

man and Calloway[35] cite m.p. 136–137°. Private communication with Dr. further confirms the higher melting point listed.

that the alpha mercurials react about five times as rapidly as the beta isomers.[2] According to Paul,[23] the furylmercuric chlorides can be determined quantitatively by titration with iodine in ethyl acetate according to the reaction:



TABLE 2. CLEAVAGE OF FURAN MERCURIALS

Mercurial	Reagent	Cleavage product (yield)	Ref.
2-Furylmercuric chloride	4% HCl (100°)	furan (82%)	2
3-Furylmercuric chloride	3.6% HCl	furan (63%)	2
5-Furfuryl-2-furylmercuric chloride	HCl (100°)	2-furfurylfuran (—)	2
5-Bromo-2-furylmercuric chloride	18% HCl	2-bromofuran (quant.)	2
5-Nitro-2-furylmercuric chloride	18% HCl	2-nitrofuran (quant.)	2
3,4-Dichloro-2-furylmercuric chloride	HCl	3,4-dichlorofuran (—)	32
5-Benzamidomethyl-2-furylmercuric chloride	HCl	2-benzamidomethylfuran (—)	20
5-Bromo-4-methyl-3-carboxy-2-furylmercuric chloride	NaOH, heat, then dil. acid and H_2S	5-bromo-4-methyl-3-furoic acid (—)	5

[15] Johnson, Van Campen and Grummitt, *J. Am. Chem. Soc.*, **60**, 111 (1938).
[16] Burtner (to G. D. Searle & Co.), U. S. Pats. 2,206,804–5 (1940); *C. A.*, **34**, 7546 (1940).
[17] Hamilton, "Furan Arsenicals," PB No. **5528**, U. S. Dept. Commerce (1942).
[18] Phatak and Laake, *J. Pharmacol. Exptl. Therap.*, **56**, 265 (1936).
[19] Ciusa, *Gazz. chim. ital.*, **55**, 385 (1925); *C. A.*, **20**, 736 (1926).
[20] Cinneide, *Proc. Roy, Irish Acad.*, **49**, B, 143 (1943).
[21] Ciusa and Bellino, *Gazz. chim. ital.*, **65**, 461 (1935); *C. A.*, **30**, 39 (1936).
[22] Gilman, Burtner and Smith, *J. Am. Chem. Soc.*, **55**, 403 (1933).
[23] Paul, *Compt. rend.*, **200**, 1481 (1935).
[24] Gilman, Burtner, Calloway and Turck, *J. Am. Chem. Soc.*, **57**, 907 (1935).
[25] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[26] Gilman and Burtner, *J. Am. Chem. Soc.*, **57**, 909 (1935).
[27] Normant, *Ann. chim.*, **17**, 335 (1942); *Bull. soc. chim.*, **7**, 373 (1940).
[28] Gilman, Van Ess and Burtner, *J. Am. Chem. Soc.*, **55**, 3461 (1933).
[29] Gilman and Burtner, *Rec. trav. chim.*, **51**, 667 (1932).
[30] Lowe and Hamilton, *J. Am. Chem. Soc.*, **57**, 2314 (1935).
[31] Vander Wal, *Iowa State Coll. J. Sci.*, **11**, 128 (1936).
[32] Gilman and Vander Wal, *Rec. trav. chim.*, **52**, 267 (1933).
[33] Klopp and Wright, *J. Org. Chem.*, **4**, 142 (1939).
[34] Lowe and Hamilton, *J. Am. Chem. Soc.*, **57**, 1081 (1935).
[35] Hoehn, *Iowa State Coll. J. Sci.*, **11**, 66 (1936).

TABLE 3. REACTION OF HALOGENS WITH FURAN MERCURIALS

Mercurial	Reagent	Product(yield)	Ref.
2-Furylmercuric chloride	I_2-KI	2-iodofuran (32%)	2
2-Furylmercuric chloride	Br_2	2-bromofuran (14.5%)	2
3-Furylmercuric chloride	I_2-KI	3-iodofuran (62%)	2
2,5-Furanbis(mercuric chloride)	I_2-KI	2,5-diiodofuran (—)	2
2,3,4,5-Furantetrakis(mercuric chloride)	I_2-KI	2,3,4,5-tetraiodofuran (67%)	14, 2, 1
5-Methyl-2-furylmercuric chloride	I_2-KI	5-methyl-2-iodofuran (48%)	2
5-Furfuryl-2-furylmercuric chloride	I_2-KI	5-furfuryl-2-iodofuran (—)	2
2,5-Dimethyl-3-furylmercuric chloride	I_2-KI	2,5-dimethyl-3-iodofuran (62%)	3
2,5-Dimethyl-3,4-furanbis(mercuric chloride)	I_2-KI	2,5-dimethyl-3,4-diiodofuran (41%)	3
5-Nitro-2-furylmercuric chloride	I_2-NaI	5-nitro-2-iodofuran (17%)	2
5-Acetoxymethyl-2-furylmercuric bromide	Br_2	5-bromofurfuryl acetate (58%)	12
5-Formyl-2-furylmercuric chloride	I_2	5-iodofurfural (46%)	12
5-Formyl-2-furylmercuric chloride	Br_2	5-bromofurfural (58%)	12
4-Carboxy-2-furylmercuric chloride (not isolated)	Br_2	5-bromo-3-furoic acid (—)	4
4-Carbomethoxy-3-methyl-2-furylmercuric chloride	Br_2	methyl 5-bromo-4-methyl-3-furoate (—)	5

TABLE 4. REACTION WITH COMPOUNDS CONTAINING ACTIVE HALOGEN

Mercurial	Reagent	Product (yield)	Ref.
2-Furylmercuric chloride	acetyl chloride	methyl 2-furyl ketone (21%)	2, 25
2-Furylmercuric chloride	benzoyl chloride	none isolated	2
2-Furylmercuric chloride	furoyl chloride	none isolated	2
3-Furylmercuric chloride	acetyl chloride	none isolated	2
2,5-Dimethyl-3-furylmercuric chloride	acetyl chloride	methyl 2,5-dimethyl-3-furyl ketone (22%)	25
2,5-Furanbis(mercuric chloride)	benzoyl chloride	2,5-dibenzoylfuran (trace)	2
5-Bromo-2-furylmercuric chloride	acetyl chloride	methyl 5-bromo-2-furyl ketone (—)	2
5-Nitro-2-furylmercuric chloride	acetyl chloride	none isolated	2
2-Furylmercuric chloride	furfuryl chloride	2-furfurylfuran (9.5%)	2
2-Furylmercuric chloride	benzyl chloride	none isolated	2

Gilman and Wooley and Wright[36] found that ketene reacts with the mercurials to give the corresponding methyl ketone. In this manner, they prepared 2- and 3-furyl methyl ketone and 2,5-diacetylfuran. The reaction is complicated by ketene polymerization, but it has since been observed[12] that this annoying side-reaction can be minimized by using chloroform or carbon tetrachloride as a solvent.

The use of furylmercuric chlorides as intermediates for the synthesis of other metallofurans is considered later in this chapter under the appropriate derivatives.

Biological Activity

A number of furan mercurials have antiseptic value as shown by Phatak and Laake,[18, 37, 38] who assigned the following descending order of bacteriostatic activity: 5-nitro-2-furylmercuric chloride, 2-furylmercuric chloride, 2-furylmercuric nitrate, 5-bromo-2-furylmercuric chloride, 5-methyl-2-furylmercuric chloride, 5-*t*-butyl-2-furylmercuric chloride. Both phenylmercuric nitrate and chloride were observed to be stronger germicides than the analogous furan types. Patents have been issued to Burtner[16] dealing with the use of furylmercuric chlorides, di-2-furylmercury and 2-furylmercuric hydroxide (Furmerane) as antiseptics.

Borzini *et al.*[39] tested the compounds derived by the action of mercuric chloride on furfural and furfuryl alcohol as preventatives against *Tilletia tritici* (wheat smut).

Furan Arsenicals

Arsenic derivatives of furan types were first reported in 1935, when Lowe and Hamilton[34] placed 2-furylmercuric chloride (1.33 moles) in reaction with arsenic trichloride (1 mole) in refluxing benzene. Mercuric chloride precipitated in almost the theoretical quantity, leaving a mixture of 2-furyldichloroarsine (I), di-2-furylchloroarsine (II), and tri-2-furylarsine (III). After several fractional distillations under reduced pressure, however, the combined yield of pure furan arsenicals was only about five per cent of the calculated amount. In addition, the products were observed to be quite unstable, the carbon-arsenic bond of I and II, for example, being subject

[36] Gilman, Wooley and Wright, *J. Am. Chem. Soc.*, **55**, 2609 (1933).
[37] Phatak and Laake, *J. Pharmacol. Exptl. Therap.*, **58**, 155 (1936).
[38] Handley, Phatak and Laake, *Univ. Calif. Pub. Pharmacol.*, **1**, 175 (1939); *C. A.*, **33**, 8802 (1939).
[39] Borzini and Marini-Bettolo, *Ricerca sci.*, **10**, 878 (1939); *C. A.*, **34**, 4853 (1940); Borzini, *Bol. staz. patol. vegetale*, **18**, 367 (1940); *C. A.*, **35**, 564 (1941); Borzini and Ciferri, *Ist. botan. univ. lab. crittogam. Pavia Atti (5)*, **3**, 243 (1947); *C. A.*, **43**, 8595 (1949).

to facile cleavage by the action of boiling water or alcohol. III is more stable, and can be steam-distilled, but even here the C-As linkage is much more easily ruptured than that of the related triphenylarsine.

Duplication of this synthesis revealed that repeated distillation of the arsenicals not only fails to effect purification, but brings about a marked change in the relative proportions of I, II and III.[40] Étienne[41, 42, 43] suggested that the arsenicals exist in equilibrium with arsenic trichloride. The latter, and III, are formed at the expense of I and II, the disproportionation being particularly favored by distillation conditions since the volatile arsenic trichloride is thereby removed from the medium. Hamilton[40] proposed the following equilibria for the system, and showed that the reactions involved are catalyzed by mercuric chloride which was found to be present

$$\underset{\text{I}}{2(C_4H_3O)AsCl_2} \rightleftharpoons \underset{\text{II}}{(C_4H_3O)_2AsCl} + AsCl_3$$

$$2\ \text{II} \rightleftharpoons \underset{\text{III}}{(C_4H_3O)_3As} + \text{I}$$

$$\text{I} + \text{II} \rightleftharpoons \text{III} + AsCl_3$$

in the distillates. In the absence of mercuric chloride, very little decomposition or disproportionation of the arsenicals takes place during distillation at reduced pressure. III may be obtained in 59 per cent yield by interaction of three moles of 2-furylmercuric chloride with one mole of arsenic trichloride. By steam distillation from aqueous sodium carbonate, the product is freed from mercuric chloride following which, equilibration of the pure III with arsenic trichloride gives rise to a mixture of I and II which may be recovered in reasonably pure state by fractional distillation.[40, 17, 41]

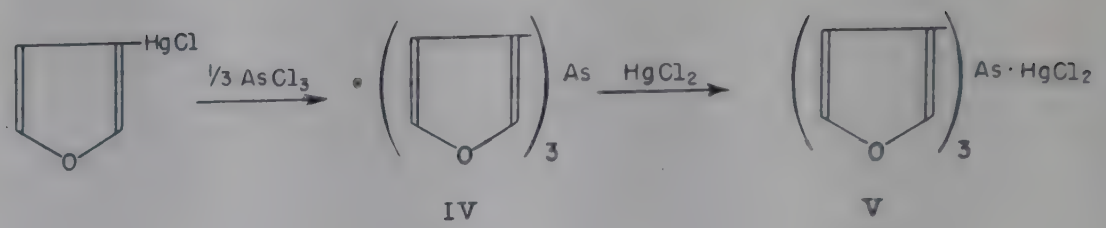
The mercurial procedure has also been employed for the synthesis of other furan arsenicals. Thus, 3-furylmercuric chloride has been converted into tri-3-furylarsine, IV, the reaction proceeding less rapidly than with the isomeric 2-furylmercuric chloride.[8] With one equivalent of mercuric chloride in alcohol, IV gives the addition compound tri-3-furylarsine-(mercuric chloride), V (m.p. 152–153°), in which reaction IV resembles triphenylarsine. Conversely, the 2-isomer (III) is cleaved under these conditions to form 2-furylmercuric chloride. Iodination of III gives rise to 2-iodofuran.[34] Similar replacement of arsenic by mercury was observed with

[40] Morgan, Cragoe, Elpern and Hamilton, *J. Am. Chem. Soc.*, **69**, 932 (1947).
[41] Étienne, *Compt, rend.*, **221**, 562 (1945).
[42] Étienne, *Compt. rend.*, **221**, 628 (1945).
[43] Étienne, *Bull. soc. chim. France*, **1946**, 669.

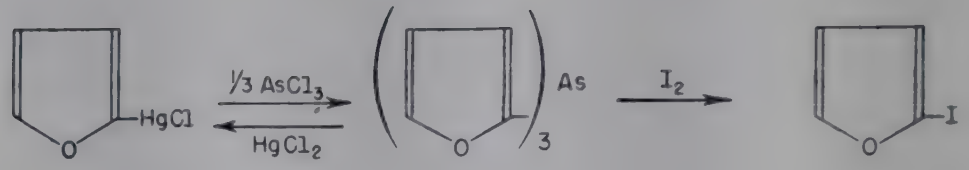
TABLE 5. FURAN ARSENICALS

Arsenical	Physical constants (°C.)	Preparation (yield)	Ref.
Derivatives of furan (R is 2-furyl)			
2-Furyldichloroarsine ($RAsCl_2$)	b.p. 102–103 (18 mm.) d_4^{20} 1.817, d_4^{25} 1.930 n_D^{20} 1.6134	a) $RHgCl + AsCl_3$ (—) b) $R_3As + AsCl_3$ (10.6%)	34, 41, 45, 17, 40
2,5-Furanbis(dichloroarsine) ($Cl_2As—C_4H_2O—AsCl_2$)	—	2,5-$ClHg—C_4H_2O—HgCl + AsCl_3$ (—)	34
Di-2-furylchloroarsine (R_2AsCl)	b.p. 122–127 (1 mm.), 152–154 (18 mm.) d_4^{20} 1.598, d_4^{25} 1.717 n_D^{20} 1.6153	a) $RHgCl + AsCl_3$ (—) b) $R_3As + AsCl_3$ (36%)	34, 41, 45, 17, 40
Tri-2-furylarsine (R_3As)	m.p. 33.5, 35 b.p. 153 (3 mm.), 158–159 (12 mm.)	a) $RHgCl + AsCl_3$ (59%) b) $RMgBr + AsCl_3$ (—) c) $RBr + AsCl_3 + Na$ (—)	34, 41, 45, 17, 40
Tri-2-furylarsine dichloride (R_3AsCl_2)	m.p. 128–129, 132	$R_3As + Cl_2$ (—)	30, 42, 46
Tri-3-furylarsine	—	3-$C_4H_3O—HgCl + AsCl_3$ (36%)	8
2-Furyldicyanoarsine [$RAs(CN)_2$]	m.p. 105	$RAsCl_2 + AgCN$ (61%)	42, 46
Di-2-furylcyanoarsine (R_2AsCN)	m.p. 32 b.p. 142–143 (2.3 mm.), 166–167 (20 mm.)	$R_2AsCl + AgCN$ (70–80%)	40, 42, 46
2-Furyldiacetoxyarsine [$RAs(OAc)_2$]	b.p. 129–130 (2 mm.) d_4^{20} 1.526; n_D^{20} 1.5245	$RAs=O + Ac_2O$ (72%)	42, 46
Di-2-furylacetoxyarsine (R_2AsOAc)	m.p. 48–50 b.p. 161–162 (10 mm.)	$R_2As—O—AsR_2 + Ac_2O$ (85%)	42, 46
2-Furylarsine oxide ($RAs=O$)	m.p. 148–150	$RAsCl_2$ + aq. Na_2CO_3 (79%)	42, 46
Tri-2-furylarsine oxide ($R_3As=O$)	m.p. 137–138	$R_3As + H_2O_2$ (51%)	42, 46
2-Furylarsine sulfide ($RAs=S$)	m.p. 125 (dec.)	$RAsCl_2 + H_2S$ (—)	34, 42, 46
2-Furanarsonic acid ($RAsO_3H_2$)	m.p. 133	$RAs=O$ + air or H_2O_2 (73%)	42, 46

Di-2-furylarsinic acid (R_2AsO_2H)	m.p. 138, 141	a) $R_3As + H_2O_2 + NaOH$ (85%) b) $R_2AsCl + NaOH + H_2O_2$ (53%)	42, 46, see also 30
2,2′-Arsenofuran (RAs=AsR)	m.p. 87	$RAs{=}O$ or $RAsO_3H_2 + H_3PO_2$ (55%)	42, 46
2,2′-Arsenofuran oxide (RAsAsR) O	m.p. 182–185	$RAs{=}AsR + O_2$ (—)	42, 46
Tetra-2-furylarshydrazine ($R_2As—AsR_2$)	m.p. 107–108	$R_2AsO_2H + H_3PO_2$ (90%)	42, 46
Bis(di-2-furylarsenic) oxide ($R_2As—O—AsR_2$)	—	R_2AsCl + aq. Na_2CO_3 (—)	42, 46
Bis(di-2-furylarsenic) sulfide ($R_2As—S—AsR_2$)	d_4^{25} 1.583	$R_2AsCl + H_2S$ (—)	34
Derivatives of substituted furans			
5-Chloro-2-furyldichloroarsine	b.p. 130–140 (15 mm.)	2,5-Cl—C_4H_2O—HgCl + $AsCl_3$ (—)	41, 45
Bis(5-chloro-2-furyl)chloroarsine	b.p. 168–170 (15 mm.)	2,5-Cl—C_4H_2O—HgCl + $AsCl_3$ (—)	42, 46
Tris(5-chloro-2-furyl)arsine	m.p. 63, 70 b.p. 190–215 (15 mm.)	2,5-Cl—C_4H_2O—HgCl + $AsCl_3$ (20%)	30, 41, 45
Tris(5-bromo-2-furyl)arsine	m.p. 105, 106	2,5-Br—C_4H_2O—HgCl + $AsCl_3$ (40%)	30, 41, 45
5-Carbomethoxy-2-bromo-3-furyldibromoarsine	m.p. 95–96	mercurial + $AsCl_3$ (50%)	8
5-Carboethoxy-2-bromo-3-furyldibromoarsine	m.p. 52–53	mercurial + $AsCl_3$ (39%)	8



IV V

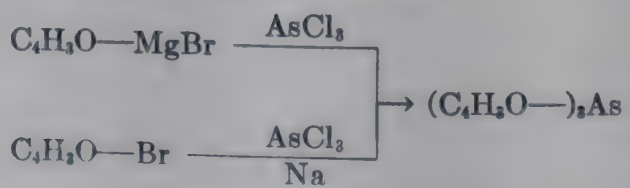


III

tris(5-chloro-2-furyl)arsine and the related bromine analog which were derived from the corresponding 5-halo-2-furylmercuric chlorides and arsenic trichloride.[30] In these instances, however, the replacement reaction goes forward less readily than in the case of III.

5-Iodo-2-furylmercuric chloride reacts readily with arsenic trichloride, but the resulting arsenicals are too unstable to air to permit isolation.[30] 5-Carbomethoxy-2-bromo-3-furylmercuric chloride resists the action of arsenic trichloride, but reacts readily with arsenic tribromide to form 5-carbomethoxy-2-bromo-3-furyldibromoarsine.[8]

Beck and Hamilton[8] were unsuccessful in attempting to prepare furan arsenicals by routes other than the mercurial procedure mentioned above. On the other hand, Étienne[41] (see also [44, 17]) reports tri-2-furylarsine by interaction of 2-furylmagnesium bromide and arsenic trichloride. He also prepared the same product by reacting 2-chloro- and 2-bromofuran with arsenic trichloride in the presence of sodium.



The chlorine atoms of the furyldichloroarsines and difurylchloroarsines are readily replaceable by oxygen and sulfur and by the cyanide group. Derivatives of pentavalent arsenic can be prepared by oxidation with chlorine, oxygen or hydrogen peroxide. These reactions are listed in Table 5.

In boiling water, furyldichloroarsine decomposes with liberation of furan. Difurylchloroarsine is also cleaved under these conditions, or in boiling

[44] Gilman and Kirkpatrick, *Proc. Iowa Acad. Sci.*, **39**, 176 (1932); *C. A.*, **28**, 6714 (1934).

alcohol, to give furan. The latter is also formed when bis(di-2-furylarsenic)-sulfide is subjected to steam distillation, and when furylarsine sulfide is refluxed with aqueous sodium hydroxide[34] (see also [41, 45, 42, 46, 8]).

The action of chlorine on furyldichloroarsine, difurylchloroarsine and trifurylarsine gives rise to 2-chlorofuran tetrachloride (2,2,3,4,5-pentachlorotetrahydrofuran) in all cases. Some trifurylarsine dichloride was also obtained in the last experiment, indicating competitive reactions involving oxidation of trivalent arsenic, addition of halogen to the furan nucleus, and scission of the carbon-arsenic linkage.[30]

When heated to 100°, furylarsenic oxide decomposes to trifurylarsine and arsenous oxide. Difurylarsinic acid resinifies under these conditions.[41, 45]

Tetrafurylarshydrazine and 2,2′-arsenofuran are rapidly oxidized by atmospheric oxygen. They may be stabilized, in solution, by the addition of a small amount of hydroquinone.[41, 45]

Compounds of Antimony

Treatment of 2-furylmercuric chloride with antimony trichloride leads only to resinous products. Tri-2-furylstibine (m.p. 46–47°; b.p. 181–182° at 17 mm.), however, has been obtained by reacting 2-chloro- or 2-bromofuran with antimony trichloride in the presence of metallic sodium. With chlorine, it is converted into trifurylantimony dichloride (m.p. 172°) in good yield. Attempts to prepare mono- and di-substituted stibines by equilibration of trifurylstibine with antimony trichloride failed due to resinification.[41, 45]

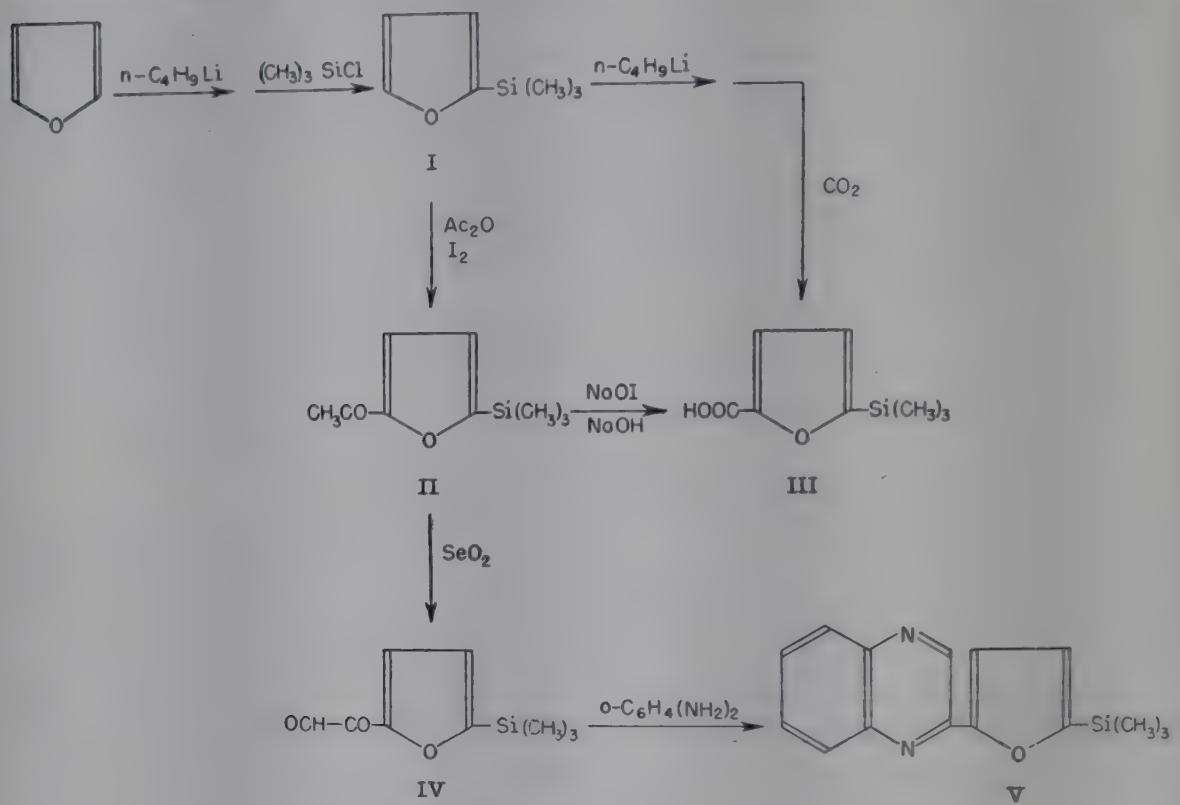
The C—Sb linkage appears to be even less stable than the C—As bond of the related arsenicals. Thus, trifurylarsine is decomposed by boiling aqueous sodium hydroxide into furan and difurylarsinic acid. Under these conditions, trifurylstibine loses all three furyl substituents as furan. It is also cleaved, to furan and antimony trichloride, by the action of dilute hydrochloric acid.

Compounds of Silicon

The only silicon derivatives of furan are those reported recently by Benkeser,[47, 48] who obtained 2-furyltrimethylsilane, I (b.p. 124–125° at 750 mm.; d_4^{20} 0.880; n_D^{20} 1.4470), in 52 per cent yield by refluxing furan with an ethereal solution of butyllithium and then with trimethylchlorosilane. Acetylation of I with acetic anhydride in the presence of iodine gives rise to 5-trimethylsilyl-2-furyl methyl ketone, II (b.p. 78.5–79° at 3–4 mm.;

[45] Étienne, *Bull. soc. chim. France*, **1947**, 50.
[46] Étienne, *Bull. soc. chim. France*, **1947**, 47.
[47] Benkeser and Currie, *J. Am. Chem. Soc.*, **70**, 1780 (1948).
[48] Benkeser and Landesman, *J. Am. Chem. Soc.*, **71**, 2493 (1949).

d_4^{20} 0.978; n_D^{20} 1.4925; semicarbazone, m.p. 200–201°). Hypoiodite oxidation of II gives the corresponding carboxyfuryltrimethylsilane, III (m.p. 110–111°), which is also obtainable by treatment of I with butyllithium and subsequent carbonation. Oxidation of II with selenium dioxide gives



rise to the corresponding glyoxal derivative, IV (monohydrate, m.p. 108–114°; b.p. 71° at 0.6 mm.), which condenses with *o*-phenylenediamine to form 2-(5-trimethylsilyl-2-furyl)quinoxaline, V (m.p. 63–64°).

Compounds of Lead

The few furyllead compounds which have been described were prepared by Gilman and Towne.[49, 50] With dilute hydrochloric acid, these compounds are invariably and quantitatively cleaved to give furan and the appropriately substituted lead chloride.

Table 6. Furan Derivatives of Lead[49, 50]

Compound	M.p. (°C.)	Preparation (yield)
2-Furyltriphenyllead	166–167	$(Ph)_3PbCl$ + 2-C_4H_3O-MgI (82%)
Di-2-furyldiphenyllead	118 (dec.)	$(Ph)_2PbCl_2$ + 2-C_4H_3O-MgI (58%)
Tetra-2-furyllead	52–53	$PbCl_2$ + 2-C_4H_3O-MgI (—)
2-Furyltri-*p*-anisyllead	83	(*p*-$MeOC_6H_4)_3PbCl$ + 2-C_4H_3O-MgI (68%)
Di-2-furyldi-*p*-anisyllead	72–73	(*p*-$MeOC_6H_4)_2PbCl_2$ + 2-C_4H_3O-MgI (56%)
Di-2-furyldi-2-thienyllead	variable	$(2\text{-}C_4H_3S)_2PbCl_2$ + 2-C_4H_3O-MgI (62%, crude)

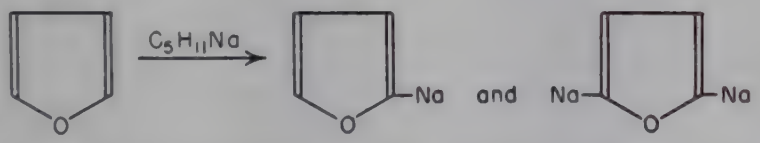
[49] Gilman and Towne, *Rec. trav. chim.*, **51**, 1054 (1932).
[50] Gilman and Towne, *J. Am. Chem. Soc.*, **61**, 739 (1939).

2-Furanboronic Acid

Johnson and his co-workers[15] synthesized 2-furanboronic acid, 2-C_4H_3O-$B(OH)_2$, in 78 per cent yield from 2-furylmagnesium iodide and methyl borate. Crystals from water melt with decomposition at 110°. If crystallized from benzene the compound melts at 121–122°. It is fairly stable in air, but discolors slowly on standing. With aqueous silver nitrate, it gives a bright orange-colored silver salt. It is readily cleaved hydrolytically to form furan; with mercuric chloride, it is converted into 2-furylmercuric chloride. Cupric chloride slowly reacts to give 2-chlorofuran and cuprous chloride. Cupric bromide reacts more rapidly with formation of 2-bromofuran. With iodine and potassium iodide, 2-iodofuran is obtained.

Alkali Metal Derivatives

Reactions leading to the formation of alkali metal derivatives of furan types are listed in Tables 7 and 8. Furan and its homologs do not react with sodium or potassium,[51, 52] although they do with liquid sodium-potassium alloy.[53] Furan reacts with ethyl-, pentyl-, phenyl-, and triphenylmethylsodium and is, therefore, more acidic than the parent hydrocarbons of these compounds. On the other hand, furan is less acidic than phenylacetylene, since it fails to react with the sodium derivative of the latter.[53] Dimetallation of furan has been accomplished with pentylsodium, subsequent carbonation of the product mixture giving rise to 2-furoic acid and 2,5-furandicarboxylic acid.[54]



The reaction of 2-methylfuran with ethyl-, phenyl-, or benzylsodium gives, on subsequent carbonation, 5-methyl-2-furoic acid, indicating nuclear substitution of an alpha hydrogen atom by sodium. Reasoning by analogy with the behavior of methylbenzenes, however, Gilman[55, 53] suggests that furfurylsodium may have been formed initially, and that this compound undergoes a modified allylic rearrangement during the carbonation step to give the observed product. There has been no confirmation of this postulate; no furylacetic acid was isolated.[53]

2-Thienylsodium reacts with furan to give, following carbonation, 2-furoic acid in 20 per cent yield.[53] No trace of 2-thenoic acid was found in this experiment. Strangely enough, however, the latter was obtained in 16 per cent yield when thiophene was placed in reaction with 2-furylsodium, and

[51] Limpricht, *Ann.*, **165**, 253 (1873).
[52] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).
[53] Gilman and Breuer, *J. Am. Chem. Soc.*, **56**, 1123 (1934).
[54] Morton and Patterson, *J. Am. Chem. Soc.*, **65**, 1346 (1943).
[55] Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).

subsequently carbonated. Furoic acid may also have been formed in this experiment.

2-Furyllithium, derived from furan and butyl- or phenyllithium[56] has been

TABLE 7. THE ACTION OF ALKALI METALS ON FURANS

Compound	Metal	Result*	Ref.
Furan	Na or K	no reaction	51
Furan	Na-K alloy	2-furylpotassium (sodium)	53
2-Methylfuran	Na or Li	no reaction	53
2-Methylfuran	Na-K alloy	5-methyl-2-furylpotassium (sodium)	53
2-Chlorofuran	Na	no reaction	52
3-Chlorofuran	Na	no reaction	52
2-Bromofuran	Na	no reaction	52
3-Bromofuran	Na	no reaction	52
3-Iodofuran	Na-K alloy	3-furylpotassium (sodium)	59
3,4-Dichlorofuran	Na	no reaction	52
Di-2-furylmercury	Na	2-furylsodium	53

* Where reaction occurred, the products were actually isolated as the corresponding furoic acids resulting from carbonation.

TABLE 8. REACTIONS OF FURANS WITH ALKALI METAL DERIVATIVES

Compound	Metallating reagent	Product (yield) (following carbonation)	Ref.
Furan	C_2H_5Na	2-furoic acid (15–25%)	53
Furan	$C_5H_{11}Na$	2-furoic acid (27%) + 2,5-furandicarboxylic acid (6.5%)	54
Furan	$C_6H_5CH_2Na$	2-furoic acid (58%)	53
Furan	$(C_6H_5)_3CNa$	2-furoic acid (—)	53
Furan	C_6H_5Na	2-furoic acid (5–15%)	53
Furan	$2\text{-}C_4H_3S\text{—}Na$	2-furoic acid (20%)	53
Furan	$C_6H_5C{\equiv}CNa$	no reaction	53
Furan	C_4H_9Li	*	47
Furan	C_6H_5Li	2-furoic acid (40%)	56
2-Methylfuran	$C_6H_5CH_2Na$	5-methyl-2-furoic acid (21%)	53
2-Methylfuran	C_6H_5Na	5-methyl-2-furoic acid (7.5%)	53
2-Methylfuran	C_4H_9Li	5-methyl-2-furoic acid (17%)	56
2-Methylfuran	C_6H_5Li	5-methyl-2-furoic acid (29%)	56
2-Furyltrimethylsilane	C_4H_9Li	5-trimethylsilyl-2-furoic acid (62%)	47
2,4,5-Triphenyl-3-chlorofuran	C_4H_9Li	2,4,5-triphenyl-3-furoic acid (14%)	60, 61
2,4,5-Triphenyl-3-bromofuran	C_4H_9Li	2,4,5-triphenyl-3-furoic acid (66%)	60, 61

* The product was treated with trimethylchlorosilane to give 2-furyltrimethylsilane in 52% yield.

[56] Gilman and Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939).

used as an intermediate for the preparation of furylsilanes,[47] and of tetra-2-furylgermanium (m.p. 99–100°; b.p. 163° at 1 mm.).[57, 58]

Furylmagnesium Halides

As can be seen from the data given in Table 9, the halogen-substituted furans are quite unreactive toward magnesium. For example, Allen and Rosener[62] were unsuccessful in attempting to prepare a Grignard reagent from 2,4,5-triphenyl-3-bromofuran and related types,[a] the bromine atom

Table 9. Reaction of Magnesium with Halofurans

Halofuran	Reagent	Result	Ref.
2-Bromofuran	Mg, or act. Mg	no reaction	52
2-Bromofuran	act. Mg-Cu alloy	2-furylmagnesium bromide	52
2-Iodofuran	Mg	2-furylmagnesium iodide	63, 64, 65, 15
3-Iodofuran	Mg, or act. Mg	no reaction	2
2,5-Diiodofuran	act. Mg-Cu alloy	5-iodo-2-furylmagnesium iodide	66
5-Methyl-2-iodofuran	Mg	5-methyl-2-furylmagnesium iodide	2, 65
2,4,5-Triphenyl-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-*p*-tolyl-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-(3,4-dimethylphenyl)-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-*p*-anisyl-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-*p*-chlorophenyl-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-*p*-bromophenyl-3-bromofuran	Mg	no reaction	62
2,4-Diphenyl-5-(4-chloro-3-methylphenyl)-3-bromofuran	Mg	no reaction	62

[a] Lutz and Smith[63] were successful in preparing 2,5-diphenyl-3-furylmagnesium bromide from 2,5-diphenyl-3-bromofuran by means of a Grignard exchange reaction using methylmagnesium iodide under special conditions.

[57] Leeper, *Iowa State Coll. J. Sci.*, **18**, 57 (1943).
[58] Gilman and Leeper, *J. Org. Chem.*, **16**, 466 (1951).
[59] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 2893 (1933).
[60] Melstrom, *Iowa State Coll. J. Sci.*, **18**, 65 (1943).
[61] Gilman and Melstrom, *J. Am. Chem. Soc.*, **68**, 103 (1946).
[62] Allen and Rosener, *J. Am. Chem. Soc.*, **49**, 2110 (1927).
[63] Lutz and Smith, *J. Am. Chem. Soc.*, **63**, 1148 (1941).
[64] Gilman, Mallory and Wright, *J. Am. Chem. Soc.*, **54**, 733 (1932).
[65] Gilman and Franz, *Rec. trav. chim.*, **51**, 991 (1932).
[66] Zoellner, *Iowa State Coll. J. Sci.*, **9**, 213 (1934).

being relatively inert. Even with the simpler 2-bromofuran, special conditions were required in order to effect reaction. Thus, Shepard, Winslow and Johnson[52] reported failure of this bromide to react with ordinary magnesium, or with magnesium activated by heating with iodine. Using an activated magnesium-copper alloy, however, they were able to prepare 2-furylmagnesium bromide, the first Grignard reagent in the furan series.

The simple iodofurans are more reactive than the chloro and bromo derivatives. 2-Furylmagnesium iodide, for example, is formed in 95 per cent yield from 2-iodofuran and magnesium[64, 65]; 5-methyl-2-furylmagnesium iodide is similarly derived from 5-methyl-2-iodofuran.[2, 66]

The furan Grignard reagents exhibit the expected reaction characteristics, although some abnormality has been observed in the case of 5-iodo-2-furylmagnesium iodide, which is readily obtained from 2,5-diiodofuran.[67] With methyl sulfate, this Grignard is converted into 2-iodofuran instead of the anticipated 5-iodo-2-methylfuran.[2]

[67] Gilman and Wright, *Iowa State Coll. J. Sci.*, **5**, 85 (1931).

Chapter 7

FURFURYL ALCOHOL AND OTHER FURAN ALCOHOLS

With only a few exceptions, all of the carbinols containing a furan nucleus are considered here. The exceptions include the nuclear nitro- and halogen-substituted types (Chapters 4 and 3), and the furyl-glycols which, for convenience, were included in Chapter 9 in connection with the discussion of the behavior of furfural. Also dealt with in this chapter are the functional derivatives of the alcohols, esters, ethers, halides, amines, mercaptans, etc.

Furfuryl Alcohol and Its Derivatives

Furfuryl alcohol (2-furylcarbinol) is produced commercially by catalytic hydrogenation of furfural, a subject which has received a great deal of attention from numerous investigators (see Chapter 15). It is also obtainable from the aldehyde, together with 2-furoic acid, by the well-known Cannizzaro reaction (p. 379). Natural sources include roasted coffee oil[1, 2, 3, 4, 5], chicory oil[6], yellow leaf tobacco [7, 8] and heated skim milk[9, 10].

The pure alcohol is a colorless liquid of mild odor, possessing the physical properties listed in Table 1. It is miscible with water, alcohol, ether, acetone, and ethyl acetate, and is soluble in most organic solvents with the exception of the paraffin hydrocarbons. For those interested in its solvent properties, the following references may be of interest [11, 12, 13, 14, 15, 16]. For color reactions of the alcohol, see Levine and Seaman[17], Deriaz *et al.*[18], Wissell and

[1] Erdmann, *Ber.*, **35**, 1846 (1902).
[2] Erdmann, *Arch. exptl. Path. Pharm.* **48**, 233 (1902).
[3] Internationale Nahrungs- und Genussmittel Akt.-Ges., Brit. Pat. 260,960 (1925); *C. A.*, **21**, 3401 (1927).
[4] Prescott *et al.*, *Food Research*, **2**, 1, 165 (1937).
[5] Johnston and Frey, *J. Am. Chem. Soc.*, **60**, 1624 (1938).
[6] Grafe, *Biochem. Z.*, **68**, 1 (1915).
[7] Hukusima and Ooike, *J. Chem. Soc. Japan*, **61**, 1297 (1940).
[8] Hukusima and Ooike, *J. Chem. Soc. Japan*, **62**, 413 (1941).
[9] Patton and Josephson, *J. Dairy Sci.*, **32**, 222 (1949).
[10] Patton, *J. Dairy Sci.*, **33**, 324 (1950).
[11] Trickey, *Ind. Eng. Chem.*, **19**, 643 (1927).
[12] Sunier, *J. Phys. Chem.*, **35**, 1756 (1931).
[13] Hammer, *Chemistry and Industry*, **1933**, 608.
[14] Kraus, *Farben-Ztg.*, **46**, 382, 400 (1941); *C. A.*, **36**, 1175 (1942).
[15] Pollak, *Paint, Oil Chem. Rev.*, **109**, 9, 22, 54 (1946).
[16] Anon., *Plastics (London)*, **10**, 582 (1946).
[17] Levine and Seaman, *Biochem. J.*, **27**, 2047 (1933).
[18] Deriaz, Stacey, Teece and Wiggins, *J. Chem. Soc.*, **1949**, 1222.

Tollens[19] and Erdmann[20]. The ignition temperature of the alcohol, in air and in oxygen, is the subject of a report by Huff[21], and Bayan and Beati[22] (see also Nisbet[23]) have discussed its value as a motor fuel. For information relating to the velocity of sound in furfuryl alcohol, see Weissler[24].

Based on results obtained by Lecat[25], Horsley[26] reports that furfuryl alcohol distills azeotropically with water, to give a distillate boiling at 98.5°, containing 20 per cent by weight of the alcohol. More recently, reexamination of this system under conditions which minimized decomposition of the alcohol has shown that the azeotrope contains only 9–10 per cent furfuryl alcohol and boils not lower than 99.85°[27]. Vapor-liquid equilibrium data have also been determined for the following systems: furfuryl alcohol-furfural[28]; furfuryl alcohol-chloroethylbenzene-chlorostyrene[29]. For critical solution temperatures of systems of the alcohol and a variety of cyclic hydrocarbons, see Francis[30].

General Behavior

Furfuryl alcohol is a very reactive compound, and to preserve it in storage it is necessary to take certain precautionary measures, primarily maintenance of relatively low temperature, and avoidance of acidic contamination and of contact with air or oxygen. Lack of attention to such measures leads to slow deterioration of the alcohol and to formation of complex nuclear condensation products which affect its composition and properties. Thus, it is well known that furfuryl alcohol may become incompletely soluble in water on standing, a more or less gradual change brought about by resinification (page 219). The reaction responsible for this change involves intermolecular dehydration of the alcohol, and is subject to acceleration by heat and/or acidic substances. For example, thermal stability studies in glass have shown that an exposure of two hours at 200° brings about changes approximately equivalent to those observed after thirty hours at 100°.[32] In connection with acidic acceleration it is important to note that acids

[19] Wissell and Tollens, *Ann.*, **272**, 291 (1893).
[20] Erdmann, *Ber.*, **35**, 1855 (1902).
[21] Huff, *U. S. Bur. Mines, Rept. Investigations*, **3669**, 43 pp. (1942); *C. A.*, **37**, 1869 (1943).
[22] Bayan and Beati, *Chimica e industria (Italy)*, **23**, 432 (1941); *C. A.*, **36**, 7262 (1942).
[23] Nisbet, *J. Inst. Petrol.*, **27**, 293 (1941).
[24] Weissler, *J. Am. Chem. Soc.*, **70**, 1634 (1948).
[25] Lecat, *Ann. soc. sci. Bruxelles*, **55B**, 43 (1935); *C. A.*, **29**, 3889 (1935).
[26] Horsley, *Ind. Eng. Chem., Anal. Ed.*, **19**, 508 (1947).
[27] The Quaker Oats Company, unpublished work.
[28] Dunlop and Trimble, *Ind. Eng. Chem.*, **32**, 1000 (1940).
[29] Berg and Harrison (to Gulf Research and Development Co.), U. S. Pat. 2,442,229 (1948); *C. A.*, **42**, 6849 (1948).
[30] Francis, *Ind. Eng. Chem.*, **36**, 1096 (1944).
[31] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).
[32] Dunlop and Peters, *Ind. Eng. Chem.*, **34**, 814 (1942).

TABLE 1. PROPERTIES OF FURFURYL ALCOHOL

			Ref.
Specific gravity:	d_{20}^{20} 1.1351, d_4^{20} 1.1285		20, 31
Refractive index*:	n_D^{20} 1.4868, 1.4848		28, 31
Vapor pressure data:	(Temp. °C.)	mm. of Hg.	33, 34
	31.8	1	
	40	1.8	
	56.0	5	
	60	6.3	
	68	10	
	80	20.3	
	81	20	
	95.7	40	
	100	53.5	
	104.0	60	
	115.9	100	
	120	127.4	
	133.1	200	
	140	271	
	151.8	400	
	170.0	760	
Melting point:	metastable crystalline form, −29°C.		34
	stable crystalline form, −14.63°C.		
Thermochemical data† in cal./g.:			34, 35, 37
Heat of combustion:			
at constant volume		6206.6	
at constant pressure		6209.6	
Specific heat:			
liquid at −20°C.		0.450	
liquid at 0°C.		0.472	
liquid at 25°C.		0.502	
stable crystalline form at −40°C.		0.256	
stable crystalline form at −20°C.		0.278	
Heat of fusion:			
stable crystalline form		31.8	

* In our experience we find n_D^{20} 1.4868–1.4870 and n_D^{25} 1.4843–1.4845.[28, 32] The usual method of purification, repeated fractional distillation, can give a fallacious idea of purity, inasmuch as slight polymerization, with attendant formation of trace amounts of water and formaldehyde, occurs even on distillation under vacuum. This may account for the lack of agreement in several of the constants reported in the literature.

† For heat of solution data, see [35, 36].

[33] Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

[34] Parks, G. S., private communication; Parks, Mosley and Peterson, *J. Chem. Phys.*, **18**, 152 (1950).

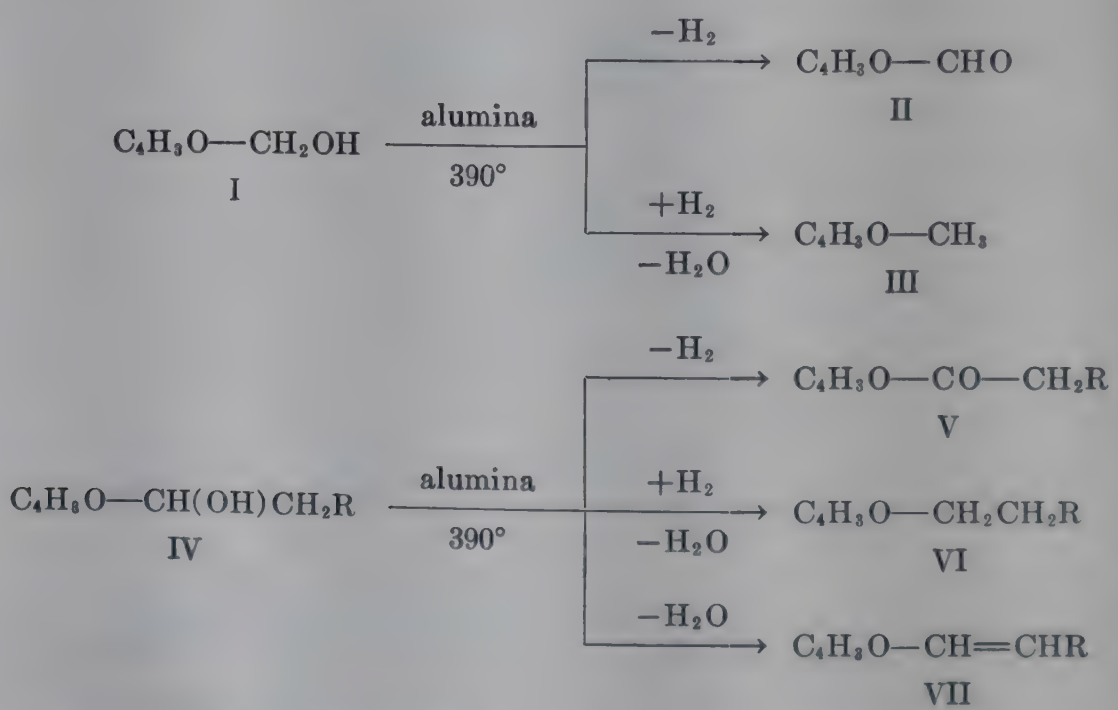
[35] Andre, *Compt. rend.*, **128**, 1035 (1899).

[36] Schmidt, Sottysiak, Tajkowski and Denison, *J. Am. Chem. Soc.*, **63**, 2669 (1941).

[37] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).

may be formed *in situ* as a consequence of autoxidation (page 220). Fortunately, both resinification and autoxidation are inhibited by basic compounds, and in most instances, satisfactory preservation of the alcohol can be achieved by the addition of a small amount of *n*-butylamine, or piperidine, or the like.[32] Aged or darkened furfuryl alcohol can be purified and is reported to be stabilized by distillation over a small quantity of inorganic base.[38]

When furfuryl alcohol (I) is passed over alumina at *ca.* 390° under conditions which exclude oxygen, furfural (II) and 2-methylfuran (III) may be isolated from the product mixture.[39, 40] In the same way, alkylfurylcarbinol (IV) gives rise to notable quantities of the corresponding alkylfuryl ketone (V) and alkylfuran (VI) in addition to the expected dehydration product, vinylfuran or its homologs, VII. Paul[39, 40] explained these results by postulating that, in part, the alcohol undergoes dehydrogenation with formation of the appropriate carbonyl compound, and cited the formation of III from I as evidence that VI does not, in this reaction, arise by reduction of VII, but rather is produced by direct reduction of the alcohol group of IV.

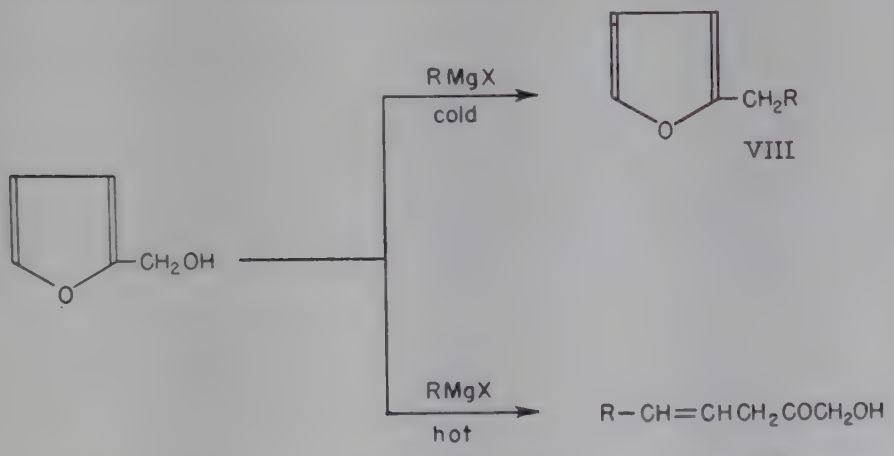


Heating furfuryl alcohol in the liquid phase at 150° in the presence of Raney nickel, likewise results in the formation of methylfuran (28 per cent), together with furfural (19 per cent) and furan (29 per cent), the last named product presumably arising by decomposition of furfural

[38] Farber, U. S. Pat. 2,486,738 (1949); *C. A.*, **44**, 2565 (1950).
[39] Paul, *Compt. rend.*, **200**, 1118 (1935).
[40] Paul, *Bull. soc. chim.*, [5] **2**, 2220 (1935).

with liberation of carbon monoxide.[41, 42] The same products were obtained by Kline and Turkevich[43] when vapors of the alcohol and ammonia were passed over alumina and chromia-alumina contact surfaces at elevated temperature. These investigators had hoped to effect conversion to pyridine, but found no evidence of reaction with ammonia under any of the conditions employed (see also [44]).

Catalytic hydrogenation of furfuryl alcohol can be carried out so as to obtain the saturated alcohol, tetrahydrofurfuryl alcohol, or straight chain compounds as a result of hydrogenolysis of the nucleus, or it may be restricted to the reduction of the alcohol group (Chapter 15). Reduction with sodium and alcohol in liquid ammonia gives methylfuran (20 per cent) with two-fifths of the original furfuryl alcohol being recoverable.[45] According to Kuznetsov[46] organomagnesium compounds also reduce the alcohol. When this reaction is conducted in xylene, in the cold, he reports the formation of alkylfurans, VIII, by replacement of the hydroxyl by the radical of the particular Grignard reagent employed.[a] At elevated temperatures (refluxing xylene) cleavage of the nucleus occurs to give compounds which Kuznetsov[46] (see also p. 253) has formulated as unsaturated α-ketols, IX.



Furfuryl alcohol reduces aqueous potassium permanganate immediately in the cold, ammoniacal silver solution on gentle heating.[20] With alkaline

[a] Kuznetsov[46] treated furfuryl alcohol with propylmagnesium iodide in cold xylene, and reported the formation of "2-butylfuran", b.p. 160–162°. According to Gilman and Calloway[47], 2-*n*-butylfuran boils at 137–138°, and the isomeric 2-butylfurans all boil lower than this. Thus, from the data given in the abstract[46] (original reference not consulted) there would appear to be some doubt regarding the identity of Kuznetsov's product.

[41] Paul, *Compt. rend.*, **208**, 1319 (1939).

[42] Paul, *Bull. soc. chim.*, **8**, 507 (1941).

[43] Kline and Turkevich, *J. Am. Chem. Soc.*, **66**, 1710 (1944).

[44] Natta, Mattei and Bartoletti, *Chimica e industria*, **24**, 81 (1942); *C. A.*, **37**, 6261 (1943).

[45] Birch, *J. Chem. Soc.*, **1945**, 809.

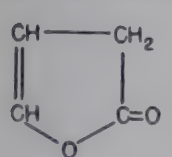
[46] Kuznetsov, *J. Gen. Chem. U. S. S. R.*, **16**, 187 (1946); *C. A.*, **41**, 443 (1947).

potassium ferricyanide, Brown[48] oxidized the alcohol to furoic acid in about 20 per cent yield. In the vapor phase with oxygen over copper oxide at 175–185°, Zetzsche and Zala[49] (see also [50]) obtained furfural in 76 per cent yield; over miscellaneous vanadium oxide catalysts, Milas and Walsh[51] report relatively low yields of maleic acid. The complete degradation of the alcohol by fuming nitric acid has received consideration in connection with the development of rocket propellants.[52, 53]

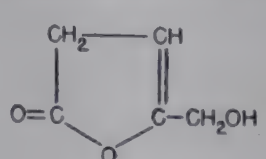
The Oppenauer oxidation has been applied to furfuryl alcohol. With *p*-benzoquinone, and aluminum phenoxide in benzene, it is converted into furfural.[54] A similar conversion occurs when the alcohol is treated with aliphatic ketones possessing the group —CH_2CO—, in the presence of aluminum alkoxides, but the resulting furfural reacts with excess ketone to form the appropriate furfurylidene compound, X.[55, 56]

$$C_4H_3O\text{—}CH_2OH + RCH_2COR' \xrightarrow{Al(OR)_3} \underset{X}{C_4H_3O\text{—}CH{=}CRCOR'}$$

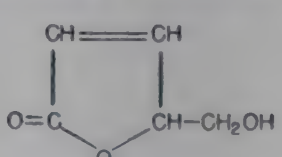
Boeseken[57] treated furfuryl alcohol with two molecular equivalents of peracetic acid (70 per cent in acetic acid) at 0–30°, and observed that more than 80 per cent was transformed into resinous products. He did succeed, however, in isolating two low molecular weight compounds. One of these analyzed for $C_4H_4O_2$ (*ca.* 4 per cent yield), and may have been 3-butenoic γ-lactone, XI. The second, $C_5H_6O_3$ (*ca.* 12 per cent yield) was presumed to be either 5-hydroxy-3-pentenoic γ-lactone, XII, or its isomer 5-hydroxy-2-pentenoic γ-lactone, XIII. With an excess of bromine in aque-



XI



XII

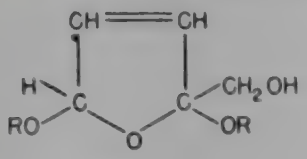


XIII

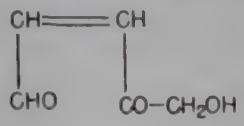
ous alkali, furfuryl alcohol is largely carbonized and destroyed.[58] Under controlled conditions, however, the action of alcoholic bromine on the

[47] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[48] Brown, *Iowa State Coll. J. Sci.*, **11**, 227 (1937).
[49] Zetzsche and Zala, *Helv. Chim. Acta*, **9**, 288 (1926).
[50] Rosenmund and Zetzsche, *Ber.*, **54**, 2033 (1921).
[51] Milas and Walsh, *J. Am. Chem. Soc.*, **57**, 1389 (1935).
[52] Seifert, Mills, and Summerfield, *Am. J. Phys.*, **15**, 121 (1947).
[53] Berggren, Ross, Young and Hawk, *J. Am. Rocket Soc.*, **73**, 17 (1948).
[54] Yamashita and Matsumara, *J. Chem. Soc. Japan*, **64**, 506 (1943); *C. A.*, **41**, 375[illegible] (1947).
[55] Batty, Burawoy, Harper, Heilbron and Jones, *J. Chem. Soc.*, **1938**, 175.
[56] Heilbron, Johnson and Jones, *J. Chem. Soc.*, **1939**, 1560.
[57] Boeseken, Vermij, Bunge and Van Meeuwen, *Rec. trav. chim.*, **50**, 1023 (1931).
[58] Panouse, *Compt. rend.*, **223**, 745 (1946); *C. A.*, **41**, 2401 (1947).

alcohol[59] (see also [60]), and on furfuryl acetate[61] proceeds by 1,4-type addition to the conjugated system of the nucleus, to give 2,5-dialkoxy-2,5-dihydrofurfuryl alcohol, XIV, and the corresponding acetate. Schenck[62] suggests that the autoxidation of furfuryl alcohol follows a similar course, whereby oxygen adds to the nucleus, possibly to form an intermediate ozonide which leads to β-(hydroxyacetyl)acrolein, XV. If formed, the latter would be difficult of isolation; should be subject to further oxidation and/or polymerization. It will be observed that XIV is a cyclic acetal of XV. The



XIV



XV

absorption of oxygen by furfuryl alcohol is accompanied by the formation of acidic products (free and potential) as shown in Table 2. This promotes formation of viscous, acid-catalyzed resinification products as a side-reaction during autoxidation, and explains the result noted by Houtz and Adkins[63] when the alcohol was stored for an extended period in the presence of a small quantity of the ozonide of diisobutylene. The data (Table 2) also demonstrate clearly the inhibition of autoxidation by tri-*n*-propylamine, and by hydroquinone as representatives of two classes of antioxidants. It is also of interest to point out that the addition of water (5 per cent) to the alcohol does not materially affect the rate of oxygen absorption.[27] This is in sharp contrast to the results obtained in studies relating to the autoxidation of furfural (see p. 386).

Furfuryl alcohol exhibits the typical behavior of a primary alcohol, and under carefully controlled conditions it can be converted into the ordinary functional derivatives, esters, ethers, etc. (see later). In general, no difficulty is encountered in carrying out syntheses in neutral or basic media. However, its reactions in acidic media are complicated by involvement of the reactive nucleus, and it is uncommonly difficult in some instances to prepare simple products in good yield. This accounts for the wide-spread utilization of basic solvent media (pyridine, or the like) in those reactions of the alcohol which require the use of acidic reagents, or which go forward with liberation of acidic products, particularly the halogen acids. Furthermore, the presence of moisture enhances the activity of acids in promoting resinification of the alcohol, hence it is important to minimize this factor, an objective difficult

[59] Fakstorp, Raleigh and Schniepp, *J. Am. Chem. Soc.*, **72**, 869 (1950).
[60] Meinel, *Ann.*, **516**, 231 (1935).
[61] Clauson-Kaas and Limborg, *Acta Chem. Scand.*, **1**, 619 (1947).
[62] Schenck, *Chem. Ber.*, **80**, 289 (1947).
[63] Houtz and Adkins, *J. Am. Chem. Soc.*, **53**, 1058 (1931).

TABLE 2. AUTOXIDATION OF FURFURYL ALCOHOL (FA)[27]

Conditions: 25-ml. samples of furfuryl alcohol were shaken in an atmosphere of oxygen at room temperature.

Oxygen Absorption (moles of O_2/liter of FA)

Time (hrs.)	FA	FA + 0.5% $(n\text{-}C_3H_7)_3N$	FA + 0.5% hydroquinone
42	0.075	—	—
74	0.250	—	—
127	0.636	—	—
162	0.840	—	—
215	0.972	—	—
264	1.084	—	0.074
330	1.229	0.019	0.117
	Acidity (equiv./liter of FA)		
0 (initial)	0.004	0.012 (alkaline)	0.005
330 (final)	0.365*	0.003 (alkaline)	0.041

* This value represents the free acidity determined by electrometric titration with standard alkali. Additionally, there was a large potential acidity (lactone products ?). Thus, when the autoxidized alcohol was permitted to stand overnight in excess aqueous alkali, back titration showed a total acidity (free plus potential) of 1.095 equiv./liter of the alcohol. This value is reasonably close to that of the oxygen uptake in moles O_2/liter of the alcohol.

of attainment, since the initial reaction leading to resin formation gives rise to water as a by-product. While disconcerting to the synthetic organic chemist, these properties in acidic medium are considered assets by the resin manufacturer, and at this point, it seems well to give some consideration to the resinification reaction.

The chief commercial outlet for furfuryl alcohol is in the plastics industry, and numerous patents have issued relating to applications in this field. These uses are discussed later (Chapter 18), but it seems worthwhile to give some attention here to the means employed to promote resinification, although there is no attempt at completeness; the patent literature on this point is voluminous.

Quite early in its history it was observed that furfuryl alcohol could be converted into dark colored, viscous or hard, resinous products by the action of acidic reagents.[64, 19, 20] In more recent times, patents were granted to Trickey and Miner[65, 66, 67] which make use of hydrochloric and sulfuric

[64] Limpricht, *Ann.*, **165**, 253 (1873).

[65] Trickey and Miner (to The Quaker Oats Co.), U. S. Pat. 1,665,235 (1928); *C. A.*, **22**, 1863 (1928).

[66] Trickey and Miner (to The Quaker Oats Co.), U. S. Pat. 1,665,236 (1928); *C. A.*, **22**, 1783 (1928).

[67] Trickey and Miner (to The Quaker Oats Co.), U. S. Pat. 1,665,237 (1928); *C. A.*, **22**, 1783 (1928).

acids as catalysts. Heberer and Marshall[68] cite the use of zinc chloride, phosphorus pentoxide, and chromic acid, while calling attention to the inhibiting action of selected solvents. Dinelli[69, 70] brought about the resinification with mercuric chloride, and with iodine. Catalysts of the Friedel-Crafts type, activated clays, and hydrofluoric acid have also been employed.[71] Meiler[72] makes use of ligninsulfonic acids, and more recently[73, 74] inorganic amine salts have been reported as latent catalysts, active on application of heat (see also [75]). The rate of resinification is, of course, accelerated by increasing the operating temperature, but beyond this, kinetic studies have revealed that the rate is a simple function of pH, at least during the early stages.[b]

Consideration of the intermediate products which have been isolated[69, 70, 32, 27] (see also [76]) gives a partial understanding of the course of the resinification. When furfuryl alcohol is heated, alone or with acidic catalysts, the first step of reaction is one of intermolecular dehydration. To some extent this gives rise to furfuryl ether, XVI, but to a greater extent dehydration follows a course which depends upon condensation between the hydroxyl group of one molecule of the alcohol with the labile, nuclear α-hydrogen

[b] These studies involved heating the alcohol at 90° with an equal volume of aqueous buffer solution (McIlvaine's standard buffer solutions) at various pH levels (2.2 to 5.38). The time required for the solution to separate into two distinct phases was noted, and considered to be a measure of the rate of resinification. A plot of the data (pH vs. log time) produced a straight line, whence $pH = \log t_s - C$ where t_s is the time for separation to occur. To determine whether the nature of the catalyst influenced the rate, the tests were repeated using aqueous solutions of specific acidic products. In all experiments wherein the latter were of pH 3 or lower insolubilization of the alcohol occurred at a rate very close to that predicted by the "buffer curve." However, in the unbuffered systems of pH > *ca.* 3 the rate was always more rapid than that predicted. This apparent anomaly is explainable in terms of the formation of levulinic acid from furfuryl alcohol (see page 224), which reaction is in competition with the resinification. When pure furfuryl alcohol was heated with an equal volume of distilled water (pH 6.3) until two layers had formed, the aqueous layer showed pH 3.2 due to the formed levulinic acid. In the buffered systems no interference was observed, because the amount of levulinic acid formed at the time of phase separation did not exceed the buffer capacity.[27]

[68] Heberer and Marshall (to Glidden Co.), U. S. Pat. 2,095,250 (1937); *C. A.*, **31**, 8761 (1937).

[69] Roberti and Dinelli, *Ann. chim. applicata*, **26**, 321 (1936).

[70] Dinelli and Marini-Bettolo, *Gazz. chim. ital.*, **71**, 117 (1941); *C. A.*, **36**, 1928 (1942).

[71] Lieber and Thorner (to Standard Oil Development Co.), U. S. Pat. 2,274,864 (1942); *C. A.*, **36**, 4707 (1942).

[72] Meiler (to Marathon Paper Mills Co.), U. S. Pat. 2,243,481 (1941); *C. A.*, **35**, 5596 (1941).

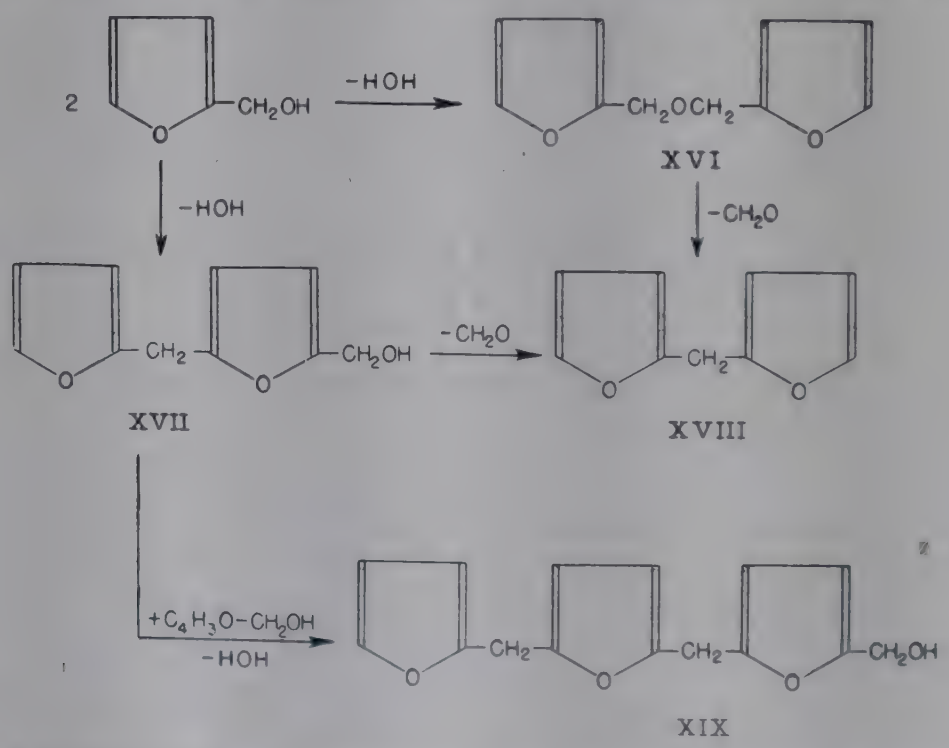
[73] The British Thomson-Houston Co., Ltd., Brit. Pat. 549,515 (1942); *C. A.*, **38**, 814 (1944).

[74] Fiedler and Holmberg (to General Electric Co.), U. S. Pat. 2,345,966 (1944); *C. A.*, **38**, 4724 (1944).

[75] Nordlander (to General Electric Co.), U. S. Pat. 2,399, 055 (1946); *C. A.*, **40**, 4251 (1946).

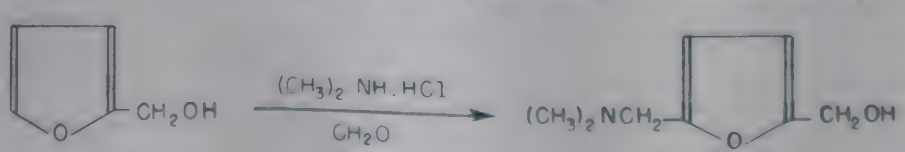
[76] Dinelli and Marini, *Gazz. chim. ital.*, **67**, 417 (1937); *C. A.*, **32**, 1261 (1938).

atom[c] of another to form 5-furfurylfurfuryl alcohol, XVII (see p. 261). Di-2-furylmethane, XVIII, has also been identified, although it is present in relatively small quantity, and presumably is formed by thermal decomposition of XVII and/or XVI. The other product of this proposed degradation, formaldehyde, has also been found in the reaction mixture, although for the most part, it is believed to have its origin in higher molecular weight condensation products. Also isolable is a compound which analyses correctly for the condensation of three molecules of furfuryl alcohol with loss of two molecules of water, and which has been assigned structure XIX (p. 261). According to this scheme, furfuryl alcohol acts as a bifunctional monomer, and in the early stages of resinification gives rise to linear condensation products composed of furan nuclei linked together by methylene bridges, and possessing a terminal hydroxymethyl group, although the latter may be lost, to a greater or lesser extent as formaldehyde, depending



upon the temperature of operation. The above diagram is intended to describe the preliminary steps of the resinification of furfuryl alcohol; the

[c] The reactivity of the 5-hydrogen atom in furfuryl alcohol in acidic medium is also apparent in its participation in the Mannich reaction with formaldehyde and amine salts. Thus, the alcohol, formaldehyde, and dimethylamine hydrochloride give rise to 5-(dimethylaminomethyl)furfuryl alcohol, in 12 per cent yield, accompanied by much resinification[77] (see p. 268). In all probability the reaction would have proceeded more smoothly in acetic acid than it did in hydrochloric acid (see [78]).



condensations leading to the formation of viscous tars and fusible, solid resins. At some advanced stage of reaction, however, the resinous mass becomes rubbery and finally sets to a hard, infusible material.[d] The reactions responsible for these changes have not been elucidated, but the following considerations have some bearing on the subject. Thus, it is known that the liberated formaldehyde can recondense,[e] and as a matter of fact, there are several patented processes wherein formaldehyde is deliberately added to modify the properties of the resin[79, 80] (see also [81]). By analogy with the acid-catalyzed condensation of formaldehyde with ethyl furoate[70] (p. 506), and with the reported behavior of pyrrole compounds,[82] the probable result of such condensation is the formation of methylene and/or oxydimethylene cross-linkages which add to the structural complexity of the final resin.[83] Another type of cross-linking of linear chains which may occur in the later stages of resinification is that involving polymerization by way of the nuclear double bonds. Indirect evidence for such is seen in the work of Norris and Terry[84] who observed that the resinification of fatty esters of furfuryl alcohol was accompanied by a decrease in the degree of unsaturation (iodine number). It is interesting to note that the course of reaction also involved deacylation of the ester, presumably by intermolecular condensation similar to that proposed above for the dehydration of the alcohol. Yet another complicating factor in the resinification of the latter, is the partial recondensation of the water liberated in the initial step, which in all probability results in cleavage of some of the furan nuclei in the resin molecule.[27] Thus, the actual structure of the completely cured resin is unknown. It is a dark colored, insoluble and infusible solid material which has

[d] The transformation to the infusible solid stage is brought about by heat and acidic catalysts. Peroxides do not appear to be effective, although driers of the type used in paints are reported to accelerate the curing of furfuryl alcohol resin in coating applications.[75]

[e] When furfuryl alcohol is completely resinified to the solid state in a sealed tube, little or no formaldehyde can be detected in the aqueous layer drawn off at the close of the experiment. Yet at almost all stages, prior to solidification, it is possible to demonstrate its presence.[27]

[77] Holdren, *J. Am. Chem. Soc.*, **69**, 464 (1947).

[78] Eliel and Peckham, *J. Am. Chem. Soc.*, **72**, 1209 (1950).

[79] Zerweck, Schubert, Heinrich and Pinten (to General Aniline and Film Corp.), U. S. Pat. 2,306,924 (1942); *C. A.*, **37**, 3533 (1943).

[80] Harvey (to Harvel Research Corp.), U. S. Pat. 2,343,972 (1944); *C. A.*, **38**, 3391 (1944).

[81] Harvey and Durst (to Harvel Research Corp.), U. S. Pat. 2,383,793 (1945); *C. A.*, **39**, 5560 (1945).

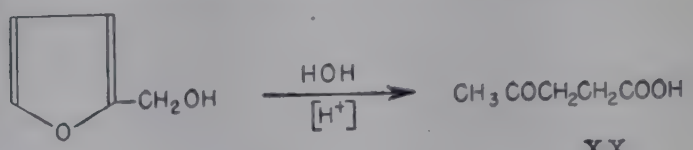
[82] Fischer and Orth, "Die Chemie des Pyrrols," Vol. I, p. 138, Leipzig, Akademische Verlagsgesellschaft M. B. H. (1934).

[83] Dunlop and Peters, in Alexander, "Colloid Chemistry," Vol. VI, p. 1058, New York, Reinhold Publishing Corp. (1946).

[84] Norris and Terry, *Oil and Soap*, **21**, 193 (1944).

found extensive application in the plastics industry because of its resistance to attack by solvents, acids and alkalies.

In the course of the resinification reaction, an increase in titratable acidity is generally observed; a consequence of competitive reaction whereby water condenses with furfuryl alcohol to form levulinic acid, XX.



XX

(For an explanation of this hydrolytic cleavage-rearrangement, the reader is referred to p. 646). Like the resinification reaction, this transformation is also catalyzed by acidic reagents, and by selection of appropriate experimental conditions, conversion of the alcohol in either direction is largely controllable. Thus, the formation of XX is minimized by operating in a non-hydroxylic medium and by removing the water of dehydration as it is formed. Conversely, treatment of the alcohol in dilute aqueous, acidic medium minimizes resinification, and relatively high yields (up to *ca.* 64 per cent of the theoretical) of XX have been obtained under such conditions[85, 27] (see also [86]). This is not surprising, since the initial step of resinification, intermolecular dehydration, is presumably bimolecular with respect to the concentration of furfuryl alcohol, whereas the rate of the reaction leading to levulinic acid is a function of the concentrations of two reactants, the alcohol and water. The system presents a difficult problem from the standpoint of kinetic studies, as is apparent in the published work of Teunissen.[87]

Attention is called to an important consequence of the varied behavior and reactivity of furfuryl alcohol. Heating induces self-condensation with elimination of water, which can be instrumental in producing levulinic acid, which in turn, accelerates both reactions. The implications go beyond resinification and levulinic acid formation; they are of great import in all preparative chemistry involving the use of furfuryl alcohol, as will be seen in the text which follows.

Functional Derivatives

Carboxylic Esters. Direct esterification of strong organic acids with furfuryl alcohol, or the use of mineral acids to catalyze reaction with weaker carboxylic acids, is precluded on account of the ease of resinification of the

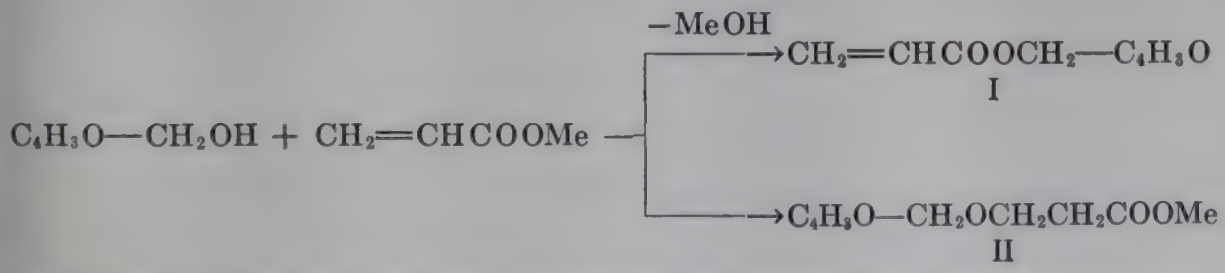
[85] Berkenheim and Dankova, *J. Gen. Chem. U. S. S. R.*, **9**, 924 (1939); *C. A.*, **34**, 368 (1940).

[86] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 19 (1942); *C. A.*, **44**, 8859 (1950).

[87] Teunissen, *Rec. trav. chim.*, **50**, 1 (1931).

alcohol. The latter complication may proceed with explosive violence under certain conditions, as in one reported attempt[88] to prepare furfuryl formate from furfuryl alcohol and formic acid (see also [70]). Subsequently[89] (see also [90]), the formic ester was synthesized in reasonable yield by treating the alcohol with acetic formic anhydride. This emphasizes the need for careful control of acidity in the preparation of carboxylic furfuryl esters. Successful operation demands the employment of techniques which insure relatively low acidity, or even a basic condition.

Zanetti[91] synthesized a number of the lower fatty esters by reacting furfuryl alcohol with the appropriate carboxylic anhydride. The Schotten-Baumann technique is also applicable to furfuryl alcohol[19, 92] but perhaps the most desirable procedure is that of alcoholysis, whereby the methyl ester of the selected acid is heated with furfuryl alcohol in the presence of a small amount of sodium furfuroxide[84, 93, 94, 95] which is readily obtained from the alcohol by the action of sodium or sodium hydride.[96] In the particular case of α,β-unsaturated carboxylic esters, the alcohol exchange reaction may be complicated by addition to the olefinic linkage. Thus, Rehberg and Fisher[97] prepared furfuryl acrylate, I, by treating the methyl ester with furfuryl alcohol and aluminum isopropoxide. On the other hand, by varying the experimental conditions, they found it possible to obtain methyl β-furfuryloxypropionate, II, b.p. 127° (12 mm.); d_4^{20} 1.1278; n_D^{20} 1.4693, or mixtures of I and II, or presumably the completely furfurylated product, furfuryl β-furfuryloxypropionate.[98, 99] Acrylonitrile adds furfuryl alcohol in a similar manner under the influence of sodium oxide or sodium hydroxide,



[88] Tobie, *News Ed. Am. Chem. Soc.*, **18**, 72 (1940).
[89] Edwards and Reeves, *J. Am. Chem. Soc.*, **64**, 1583 (1942).
[90] Frank, Davis, Drake and McPherson, *J. Am. Chem. Soc.*, **66**, 1509 (1944).
[91] Zanetti, *J. Am. Chem. Soc.*, **47**, 535 (1925).
[92] Zanetti, *J. Am. Chem. Soc.*, **47**, 1452 (1925).
[93] Swern, Jordan and Knight, *J. Am. Chem. Soc.*, **68**, 1673 (1946).
[94] Swern, Billen and Knight, *J. Am. Chem. Soc.*, **69**, 2439 (1947).
[95] Jordan and Swern, *J. Am. Chem. Soc.*, **71**, 2377 (1949).
[96] Hansley (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,267,733 (1942); *C. A.*, **36**, 2567 (1942).
[97] Rehberg and Fisher, *J. Org. Chem.*, **12**, 226 (1947).
[98] Rehberg and Dixon, *J. Am. Chem. Soc.*, **72**, 2205 (1950).
[99] Rehberg and Fisher (to the United States of America, as represented by the Secy. of Agriculture), U. S. Pat. 2,504,151 (1950); *C. A.*, **44**, 6429 (1950).

TABLE 3. FURFURYL ESTERS

Compound	Physical constants (°C.)	Ref.
Carboxylic esters		
Formic	b.p. 66.2–66.5 (16 mm.), 166.3 (760 mm.) d_4^{25} 1.1584 n_D^{25} 1.4662	89
Acetic	b.p. 67 (8 mm.), 182–182.4 (760 mm.) d_4^{20} 1.1175, d_4^{25} 1.1131 n_D^{20} 1.4627	19, 91, 31, 101, 11, 12, 102, 103, 104, 105, 106, 107, 17, 108, 109, 110, 111, 77
Chloroacetic	no constants	112
Propionic	b.p. 195–196 (762 mm.) d_4^{20} 1.1085	91
n-Butyric	b.p. 212–213 (764 mm.) d_4^{20} 1.0530	91
i-Butyric	b.p. 85–86 (15 mm.) d 1.0313	113
Valeric	b.p. 228–229 (764 mm.) d_4^{20} 1.0284	91
Palmitic	no constants	114, 84
9,10-Dihydroxystearic	two forms: m.p. 69.9–70.2 m.p. 99.0–99.3	93
Chrysanthemumic (2,2-dimethyl-3-(2-methylpropenyl)cyclopropanecarboxylic acid)	b.p. 216 (—) n_D^{22} 1.4852	115
Acrylic	b.p. 93 (16 mm.) d_4^{20} 1.1125 n_D^{20} 1.4800	97, 116
Methacrylic	b.p. 80–82 (5 mm.) d_{20} 1.055	117
10-Undecenoic	b.p. 164–165 (4.3 mm.) d_4^{20} 0.9675 n_D^{20} 1.4671	95
Oleic	b.p. 195 (0.1 mm.) d_4^{30} 0.9295 n_D^{30} 1.4681	94
Benzoic	b.p. 275–285 (atm.) d_{20}^{20} *ca.* 1.1766	19
p-Nitrobenzoic	m.p. 75–77	118
3,5-Dinitrobenzoic	m.p. 79–81	9
Phthalic (mono ester)	m.p. 85	119
Carbamic esters and related types		
Urethan	m.p. 50	20
Phenylurethan	m.p. 43–45	9, 120
p-Aminophenylurethan	m.p. 114	121
p-Nitrophenylurethan	m.p. 163	121
Diphenylurethan	m.p. 98	119, 20
1-Naphthylurethan	m.p. 129–130	122, 119; see also 123
Allophanate	m.p. 167.5, 170 (dec.)	124, 120

or trimethylbenzylammonium hydroxide, to give β-furfuryloxypropionitrile (furfuryl 2-cyanoethyl ether, see Table 4).[100]

The known carboxylic furfuryl esters are listed in Table 3. Those of the lower fatty acids are colorless, oily liquids of pleasant odor. For attempted preparation of the pyruvic ester, see Wienhaus.[120] The acetate is reported to possess growth-promoting activity in plant root formation[125] (see also [89]), and has been tested as a solvent for naphthalene,[12] dichlorofluoromethane,[108] various gums and resins,[11] and for the extraction of penicillin.[126] Furfuryl oleate and undecenoate are relatively inactive in peroxide-catalyzed polymerizations[94, 95] (see also [97, 84]). Furfuryl esters of rosin acids were prepared by Borglin.[127] The crotonate[128] and phthalate[129] have been employed in the preparation of resinous coatings.

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[100] Bruson (to The Resinous Products and Chemical Co.), U. S. Pat. 2,280,790 (1942); *C. A.*, **36,** 5588 (1942).

[101] Mathews and Fehlandt, *J. Am. Chem. Soc.*, **53,** 3212 (1931).

[102] Sunier, "Organic Syntheses," Coll. Vol. I, 279, New York, John Wiley and Sons, Inc. (1932).

[103] Guainazzi, *Pitture e vernici*, **4,** 181 (1948); *C. A.*, **43,** 4252 (1949).

[104] Gilman and Wright, *J. Am. Chem. Soc.*, **53,** 1923 (1931).

[105] Mowry, *J. Am. Chem. Soc.*, **69,** 573 (1947).

[106] Bitler and Nicholl (to Kay-Fries Chemical, Inc.), U. S. Pat. 2,406,657 (1946); *C. A.*, **41,** 309 (1947).

[107] Bitler and Nicholl (to Kay-Fries Chemicals, Inc.), U. S. Pat. 2,433,645 (1947); *C. A.*, **42,** 2137 (1948).

[108] Zellhoefer, Copley and Marvel, *J. Am. Chem. Soc.*, **60,** 1337 (1938).

[109] Wolford, *Am. Perfumer*, **21,** 75 (1926).

[110] Matsuno and Han, *Bull. Chem. Soc. Japan*, **9,** 327 (1934); *C. A.*, **28,** 7160 (1934).

[111] Gordy and Stanford, *J. Chem. Phys.*, **8,** 170 (1940).

[112] Borglin (to Hercules Powder Co.), U. S. Pat. 2,410,197 (1946), *C. A.*, **41,** 1249 (1947).

[113] Nakai, *Biochem. Z.*, **152,** 258 (1924); *C. A.*, **19,** 2807 (1925).

[114] Tatiiri, *J. Chem. Soc. Japan*, **60,** 442 (1939); *C. A.*, **35,** 5091 (1941).

[115] Harvill, *Contrib. Boyce Thompson Inst.*, **10,** 143 (1939).

[116] Rehberg and Fisher (to the United States of America, as represented by the Secy. of Agriculture), U. S. Pat. 2,433,866 (1948); *C. A.*, **42,** 1969 (1948).

[117] E. I. du Pont de Nemours & Co., *Ind. Eng. Chem.*, **28,** 1160 (1936).

[118] Kleene and Fried, *J. Am. Chem. Soc.*, **62,** 3516 (1940).

[119] Brown, Gilman and Van Peursem, *Iowa State Coll. J. Sci.*, **6,** 133 (1932).

[120] Weinhaus *Ber.*, **53,** 1656 (1920).

[121] Welvart, *Bull. soc. chim. France*, **1949,** 330.

[122] Bickel and French, *J. Am. Chem. Soc.*, **48,** 747 (1926).

[123] Neuberg and Hirschberg, *Biochem. Z.*, **27,** 339 (1910).

[124] Grandière, *Bull. soc. chim.*, **35,** 187 (1924).

[125] Traub, *Proc. Am. Soc. Hort. Sci.*, **35,** 438 (1938).

[126] Rowley, Steiner and Zimkin, *J. Soc. Chem. Ind. London*, **65,** 237 (1946).

[127] Borglin (to Hercules Powder Co.), U. S. Pat. 2,012,622 (1935); *C. A.*, **29,** 7102 (1935).

[128] D'Alelio (to General Electric Co.), U. S. Pat. 2,260,005 (1942); *C. A.*, **36,** 858 (1942).

[129] Muller and Schwartz (to Driwear, Inc.), U. S. Pat. 2,253,192 (1941); *C. A.*, **35,** 8318 (1941).

TABLE 4. FURFURYL ETHERS

Ether	Physical constants (°C.)	Ref.
Methyl	b.p. 134–135 (762 mm.) d_4^{20} 1.0163, d_{20}^{20} 1.0315 n_D^{20} 1.4570	135, 136, 137 see also 19 139, 140
Ethyl	b.p. 149.5–150.5 (770 mm.) d_4^{20} 0.9844, d_{20}^{20} 0.9884 n_D^{20} 1.4523	135, 134, 141 19, 142
n-Propyl	b.p. 168–170 (767 mm.) d_4^{20} 0.9656, d_{20}^{20} 0.9722 n_D^{20} 1.4523	135, 134, 19
Allyl	b.p. 172–173 (757 mm.) d_0^{20} 1.005, d_4^{20} 1.0025 n_D^{20} 1.4718	135, 134
2-Hydroxyethyl	—	138
2-Cyanoethyl	b.p. 100–101 (1 mm.), 109–110 (2 mm.) d_{30} 1.090 n_D^{30} 1.4742	77, 100
2-(2-Cyanoethoxy)ethyl	b.p. 152–154 (1 mm.)	138
n-Butyl	b.p. 189–190 (765 mm.) d_0^{20} 0.955, d_4^{20} 0.9516 n_D^{20} 1.4522	135, 134
i-Butyl	b.p. 179–180 (755 mm.) d_0^{20} 0.946	134
i-Pentyl	b.p. 196–198 (—)	19
n-Heptyl	b.p. 99–101 (2 mm.) d_0^{20} 0.925	134
Benzyl	b.p. 108–109 (1 mm.), 118–120 (2 mm.) d_0^{20} 1.092, d_4^{20} 1.0865 n_D^{20} 1.5372	135, 134
Cinnamyl	b.p. 141–142 (1 mm.), 138–140 (2 mm.) d_0^{20} 1.075, d_4^{20} 1.0802 n_D^{20} 1.5661	135, 134
Trityl	m.p. 137–139, 139.5–140.5	143, 144
Furfuryl	b.p. 88–89 (1 mm.), 101–102 (2 mm.) d_0^{20} 1.137, d_4^{20} 1.1405 n_D^{20} 1.5088	135, 134, 145
Phenyl	b.p. 125–126 (11 mm.), 139–140 (20 mm.) d_{15}^{17} 1.124 n_D^{17} 1.5535	146, 147, 148 149
o-Tolyl	b.p. 140–141 (15 mm.) d_{15}^{16} 1.098 n_D^{16} 1.5481	146
p-Tolyl	m.p. 50.5–51	146
p-*t*-Butylphenyl	m.p. 33	146
o-Methoxyphenyl	m.p. 39.5–40	146, 147
p-Chlorophenyl	m.p. 30–31	146
p-Nitrophenyl	m.p. 98.5–99	146
2,4-Dinitrophenyl	m.p. 154.5	146

TABLE 4—*Continued*

Ether	Physical constants (°C.)	Ref.
o-Furfurylphenyl	b.p. 203–205 (16 mm.), 174–175 (3 mm.) d_{16}^{16} 1.168 n_D^{16} 1.5674	146
2-Furfuryl-4-methyl phenyl	b.p. 208 (11 mm.) $d_{16}^{11.5}$ 1.157 $n_D^{11.5}$ 1.5633	146
Diphenyldihydroanthroanthracenediol, monofurfuryl ether	m.p. 223	143
Diphenyldihydroanthroanthracenediol, difurfuryl ether	m.p. 245 (dec.)	143a

Condensation of furfuryl alcohol with carbon disulfide in strong sodium hydroxide gives rise to furfuryl sodium xanthate, $C_4H_3O—CH_2OCSSNa$, which is reported to be useful as a mineral flotation agent.[130, 131, 132, 133]

$$C_4H_3O—CH_2OH + NaOH + CS_2 \xrightarrow{-HOH} C_4H_3O—CH_2O—C(=S)—SNa$$

III

[130] Keller (to Minerals Separation North American Corp.), U. S. Pat. 1,969,269 (1934); *C. A.*, **28,** 6097 (1934); U. S. Pat. 1,833,464 (1932); *C. A.*, **26,** 951 (1932); (to The Great Western Electro-Chemical Co.), Canadian Pat. 340,262 (1932); *C. A.*, **28,** 3075 (1934).

[131] I. G. Farbenind. A.-G., French Pat. 764,099 (1934); *C. A.*, **28,** 5668 (1934).

[132] Hirschkind, Ramage and Bender (to The Great Western Electro-Chemical Co.), U. S. Pat. 2,024,924 (1935); *C. A.*, **30,** 1070 (1936).

[133] Whitmore and Lieber, *Ind. Eng. Chem., Anal. Ed.*, **7,** 127 (1935).

[134] Zanetti, *J. Am. Chem. Soc.*, **49,** 1065 (1927).

[135] Kirner, *J. Am. Chem. Soc.*, **50,** 1955 (1928).

[136] Zanetti, *J. Am. Chem. Soc.*, **49,** 1061 (1927).

[137] Adams and Marvel, "Synthesis of Miscellaneous Compounds for Possible Use as New Chemical Warfare Agents," PB No. **5564,** U. S. Dept. Commerce, 1941.

[138] Schwoegler (to Wyandotte Chemicals Corp.), U. S. Pat. 2,403,686 (1946); *C. A.*, **40,** 6499 (1946).

[139] Pummerer and Gump, *Ber.*, **56,** 999 (1923).

[140] Braun, Anton and Weissbach, *Ber.*, **63,** 2847 (1930).

[141] Gilman and Vernon, *J. Am. Chem. Soc.*, **46,** 2576 (1924).

[142] Buu-Hoi and Lecocq, *Compt. rend.*, **222,** 1441 (1946).

[143] Hurd and Thomas, *J. Am. Chem. Soc.*, **55,** 423 (1933).

[143a] Pinazzi, *Compt. rend.*, **225,** 503 (1947).

[144] Kursanov and Solodkov, *Compt. rend. acad. sci. U.R.S.S.*, **27,** 797 (1940); *C. A.*, **35,** 1770 (1941).

[145] Zanetti and Bashour, *J. Am. Chem. Soc.*, **61,** 2249 (1939).

[146] Normant, *Ann. chim.*, **17,** 335 (1942).

[147] Normant, *Bull. soc. chim.*, **7,** 373 (1940).

[148] Paul and Normant, *Compt. rend.*, **204,** 1482 (1937).

[149] Paul and Normant, *Bull. soc. chim.*, [5] **5,** 1148 (1938).

Furfuryl Ethers. The alkyl furfuryl ethers are colorless liquids of faint odor. They are strongly hygroscopic and are subject to decomposition in the presence of moisture. Like furfuryl alcohol, they undergo autoxidation with discoloration when exposed to air or oxygen, although this change may be inhibited by the addition of a small amount of hydroquinone.[134]

Several of the alkyl ethers were synthesized at a relatively early date by Wissell and Tollens[19] (see also [70]), by treatment of furfuryl alcohol with the appropriate alkyl iodide in the presence of potassium hydroxide. This reaction is also applicable to aryl halides where the halogen is activated by suitable substituent groups, e.g., 1-chloro-2,4-dinitrobenzene.[146] The methyl ether can be obtained directly from the alcohol and methyl sulfate in strong, aqueous alkali[137] (see also [140]). For the most part, however, the known furfuryl ethers have been prepared from furfuryl chloride[135] (see also [141]), bromide[134] (see also [142]), and iodide[136] by reacting an ethereal solution of the halide with the appropriate alcohol and potassium hydroxide.

Similarly, a number of aryl furfuryl ethers have been obtained from furfuryl bromide and sodium phenoxide and its derivatives.[148, 149, 146] In these instances, an important effect of medium has been observed. Thus, the reaction with sodium phenoxide in ether-alcoholic solution produces phenyl furfuryl ether, I, in 48 per cent yield, along with *o*-furfuryl-phenol (4 per cent), II, and the furfuryl ether of II, *o*-furfurylphenyl furfuryl ether (13 per cent). When the same reaction is carried out in an ether-toluene medium, the ratio of I to II is considerably changed (see below), and 2,6-difurfurylphenol is obtained as a by-product.[146, 149] Paul and Normant[148, 149]

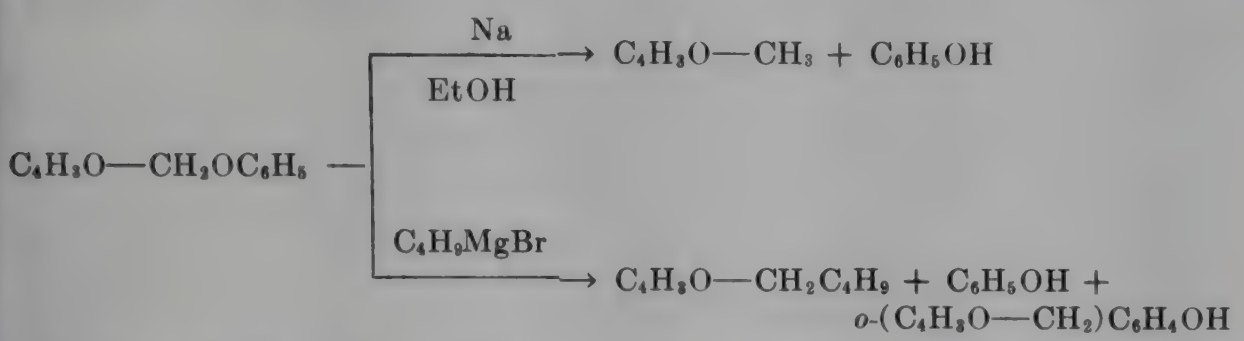
$$C_4H_3O{-}CH_2Br + C_6H_5ONa \rightarrow \underset{\text{I}}{C_4H_3O{-}CH_2OC_6H_5} + \underset{\text{II}}{o\text{-}(C_4H_3O{-}CH_2)C_6H_4OH}$$

	% Yield	
	I	II
In ether-alcohol	48	4
In ether-toluene	6	38

considered the possibility that II had its origin in I, by a rearrangement similar to that of allyl phenyl ether to allylphenol. While they were able to effect the rearrangement on strong heating, they made the observation that the mobility of the furfuryl group in I is much less than that of allyl or *t*-butyl in the corresponding phenolic ethers. Later, Normant[146] showed that I was partially converted into II by heating at 230–235° for two hours, but the transformation was accompanied by considerable decomposition as evidenced by the relatively large amount of phenol produced.

The aryl furfuryl ethers are split by the action of sodium in alcohol to give the appropriate phenol in practically quantitative yield along with 2-

methylfuran.[147, 146] They are also cleaved by the Grignard reagent but this reaction is accompanied by simultaneous, partial rearrangement. Thus, phenyl furfuryl ether and butylmagnesium bromide, in ether at reflux, give rise to phenol (40 per cent), 2-pentylfuran (31 per cent), and *o*-furfurylphenol (44 per cent). For the proposed course of these two simultaneous reactions, see Normant.[147, 146]



Furfuryl Halides. Zanetti[134] prepared furfuryl bromide and iodide from furfuryl alcohol by the action of the appropriate phosphorus trihalide in *dry* ether. Neither product was isolated but was used directly in ether solution for the synthesis of furfuryl ethers. The bromide, in ether, had been obtained earlier[150] by the less convenient method of treating furfurylmethylethylamine with cyanogen bromide. It was reported to decompose completely on attempted distillation, although it has since[145] been isolated by careful manipulation (colorless liquid, b.p. 32.5–34.5° (2 mm.); d_{20}^{20} 1.560; n_D^{20} 1.5380). It is very unstable,[f] discoloring rapidly with evolution of hydrogen bromide[g] which acts to accelerate further decomposition with *explosive violence*. Furfuryl bromide has also been prepared, in solution in carbon tetrachloride, by lateral bromination of 2-methylfuran using N-bromosuccinimide.[142]

Furfuryl chloride is also a highly reactive compound, and the early attempts[150, 141] to effect its preparation were quite unsatisfactory. However, Kirner[135] (see also [152]) obtained it in 63 per cent yield using the Darzens procedure, treatment of furfuryl alcohol with thionyl chloride in ethereal pyridine at low temperature. The pure chloride distills as a water-white liquid, b.p. 49.1–49.4° (26 mm.); d_{20}^{20} 1.1804, d_4^{20} 1.1783; n_D^{20} 1.4941. On

[f] The introduction of an electron-withdrawing substituent at the open alpha position greatly increases the stability. Compare 5-(bromomethyl)-, and 5-(chloromethyl)furfural, and also 5-nitrofurfuryl chloride with furfuryl bromide and chloride. (See [141, 151]).

[g] It is not unlikely that the furfuryl halides decompose by a mechanism similar to that proposed for the acid-catalyzed resinification of furfuryl alcohol. Where the latter undergoes an intermolecular dehydration, the former would be expected to decompose by intermolecular dehydrohalogenation (page 222).

[150] von Braun and Kohler, *Ber.*, **51**, 79 (1918).

[151] Gilman and Burtner, *Iowa State Coll. J. Sci.*, **6**, 389 (1932).

[152] Kyrides and Zienty, *J. Am. Chem. Soc.*, **71**, 1122 (1949).

standing, it discolors to yellow then green, and finally to a black tar.[f] Like the bromide, it must be kept free of moisture, and is preferably stored and used, in ether solution. Both halides are lachrymatory, and generally irritating to the eyes, nose and throat[153] (see also [145]).

Furfuryl silicate: This compound, the only other inorganic furfuryl ester mentioned in the literature, is reported to be useful in resin applications. It was prepared from furfuryl alcohol and ethyl orthosilicate.[154]

Kirner[135] proposed that the relative stability of the furfuryl halides is in the order: chloride > bromide > iodide. In all cases, the halogen atom is highly mobile, and Gilman and Wright[155] report that the chlorine atom in furfuryl chloride "appears to be the most active[h] chlorine attached to a carbon"; that by direct measurement it is distinctly more reactive than that in the related benzyl chloride. This probably accounts for the fact that attempts to obtain a useful Grignard reagent from furfuryl chloride have not been rewarding to date. Actually, it appears that partial conversion to furfurylmagnesium chloride does take place. However, there follows, immediately, an attack on the Grignard reagent by unchanged furfuryl chloride to give *sym*-difurylethane, I[157, 158]. Related to this is the deliberate synthesis of several 2-alkylfurans, II, and related types, by placing the appropriate organomagnesium halide[i] in reaction with furfuryl chloride[160, 161] and bromide.[162, 163] Similarly, condensation of the chloride with

[h] In a later study, Catlin[156] measured the relative reactivity of a number of RCH_2Cl compounds as indicated by the equation:

$$RCH_2Cl + KI \xrightarrow[50°]{\text{acetone}} KCl$$

Based on *n*-butyl chloride as unity, he obtained the data tabulated below. Note that saturation of the furan nucleus results in a marked loss of reactivity of the halogen.

Compound	Relative activity
furfuryl chloride	3,184
tetrahydrofurfuryl chloride	0.025
3-(2-furyl)propyl chloride	2.51
3-(2-tetrahydrofuryl)propyl chloride	1.33
5-nitrofurfuryl chloride	12,708
2-furyl chloromethyl ketone	98,230

[i] The reaction of furfuryl chloride with methylmagnesium iodide apparently takes a different course. The expected product, 2-ethylfuran, is not mentioned in the published work, which reports *sym*-difurylethane, I, in 50% yield[159].

[153] Gilman, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **6**, 137 (1932).

[154] Rust (to Montclair Research Corp.), U. S. Pat. 2,300,812 (1942); *C. A.*, **37**, 2103 (1944).

[155] Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).

[156] Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935).

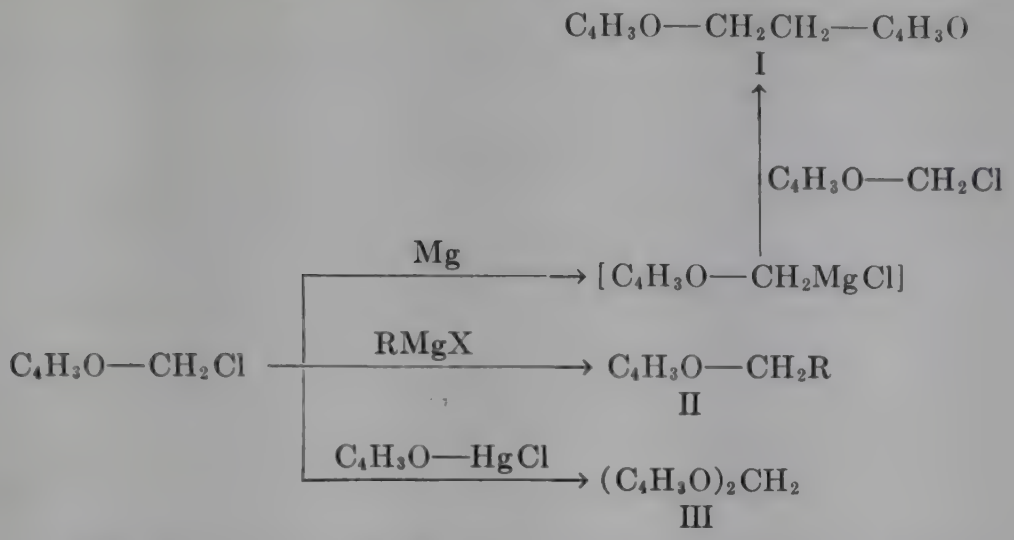
[157] Gilman and Burtner, *Iowa State Coll. J. Sci.*, **5**, 189 (1931).

[158] Gilman and Hewlett, *Rec. trav. chim.*, **51**, 93 (1932).

[159] Gilman and Wright, *J. Am. Chem. Soc.*, **55**, 3302 (1933).

[160] Reichstein, Grüssner and Zschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).

2-furylmercuric chloride gives rise to difurylmethane, III.[159] Unsuccessful

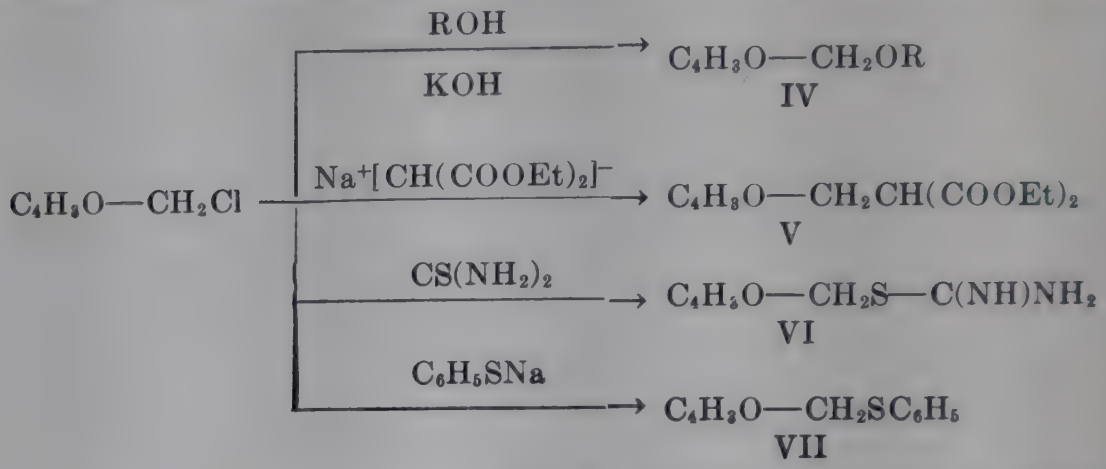


results have likewise attended efforts to prepare the Grignard reagent from 3-(2-furyl)propyl chloride which appears to be inactive toward magnesium, whereas the corresponding tetrahydrofuryl compound is quite reactive.[158, 164] However, failure in the former instance can hardly be attributed to great reactivity on the part of the chlorine atom as it was in the case of furfuryl chloride, and it is interesting to observe that the intermediate homolog, 2-furylethyl chloride, has been converted into a stable Grignard reagent.[165]

The furfuryl halides have been used in a number of the common replacement reactions of such types. Thus, as mentioned previously (page 230), treatment of an ethereal solution of the chloride with alcohol and powdered potassium hydroxide, under completely anhydrous conditions, gives rise to the corresponding ether, IV. The chloride has also been employed in the familiar malonic and acetoacetic ester syntheses, introduction of the furfuryl radical proceeding readily. For example, furfurylmalonic ester, V, has been obtained in 76 per cent yield by reacting an ether solution of the chloride with sodiomalonic ester in anhydrous alcohol,[166] and similar condensations have been successfully carried out in dry toluene.[167] With thiourea in acetone, furfuryl chloride forms S-furfurylisothiourea, VI[168]; with sodium phenyl mercaptide in *i*-pentyl alcohol, furfuryl phenyl sulfide, VII, is obtained.[169] For the reaction of furfuryl chloride and bromide with ammonia and amines, see page 235; for their use in the synthesis of furfurylbarbituric

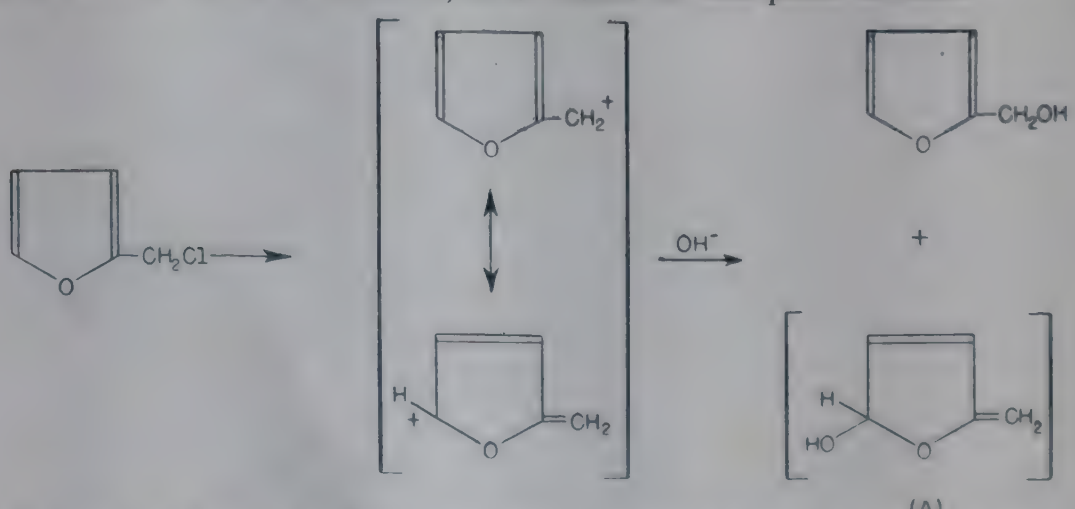
[161] Gilman, Van Ess and Burtner, *J. Am. Chem. Soc.*, **55**, 3461 (1933).
[162] Paul, *Compt. rend.*, **200**, 1481 (1935).
[163] Woodward, *J. Am. Chem. Soc.*, **62**, 1478 (1940).
[164] Hewlett, *Iowa State Coll. J. Sci.*, **6**, 439 (1932).
[165] Amstutz and Plucker, *J. Am. Chem. Soc.*, **63**, 206 (1941).
[166] Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).
[167] Moffett, Hart and Hoehn, *J. Am. Chem. Soc.*, **69**, 1849 (1947).
[168] Sprague and Johnson, *J. Am. Chem. Soc.*, **59**, 2439 (1937).
[169] Takahashi, Saikachi, Sasaki and Kimura, *J. Pharm. Soc. Japan*, **69**, 289 (1949); *C. A.*, **44**, 5374 (1950).

acids, see [170]. In these reactions, all conducted in organic solvent medium,



replacement of the halogen takes place in position. Similarly, treatment of furfuryl chloride with sodium thiocyanate in acetone is reported to give furfuryl thiocyanate, b.p. 111.5–112.5° (27 mm.); d_{20}^{20} 1.1892; n_D^{20} 1.5614.[166] On the other hand, with potassium cyanide, in water solution, the chloride is largely converted into 5-methyl-2-furonitrile rather than the normal product, furylacetonitrile. In this reaction, which is discussed in detail elsewhere (p. 550), furfuryl chloride behaves in a manner analogous to that of the allylic halides (compare 3-furylmethyl chloride, p. 264, and furfuryltrimethylammonium iodide, p. 248). This may explain the reported failure to obtain furfuryl mercaptan by the action of sodium hydrosulfide on the chloride.[j]

[j] No details of the experimental procedure appear in the published report[166]. However, if the condensation was carried out in aqueous medium, one might expect the reaction to have proceeded in a manner similar to that with aqueous potassium cyanide (p. 550). In other words, it is felt that a strongly ionic medium (water) favors "allylic" or "abnormal" reaction of furfuryl chloride. For instance, we would anticipate that the chloride, in strong aqueous potassium hydroxide, would give rise to a considerable quantity of abnormal product, A, in addition to the normal product, furfuryl alcohol. There is, however, no evidence on this point to date.



[170] Heilner (to Chemische Fabriken Joachim Wiernik & Co., Akt.-Ges.), U. S. Pat. 2,035,317 (1936); *C. A.*, **30**, 3169 (1936); Chemische Fabriken Joachim Wiernik & Co., Akt.-Ges., Brit. Pats. 486,503 and 468,555 (1937); *C. A.*, **32**, 729-730 (1938).

Amines. *Simple Furfurylamines:*

Furfurylamine is best prepared by catalytic hydrogenation of furfural (or hydrofuramide) in the presence of ammonia. By this procedure it is formed in admixture with difurfurylamine, the product distribution varying with the experimental conditions. Thus, by suitable control of the ratio of ammonia to aldehyde it is possible to obtain, at will, either the primary or the secondary amine as the major product.[171] For further discussion of this, and other catalytic hydrogenation processes for the synthesis of furfurylamines, see Chapter 15.

The primary amine is also obtainable by non-catalytic reduction of suitable furan compounds. Thus, furfural oxime gives furfurylamine on treatment with sodium amalgam,[172, 173] ammonium amalgam,[174] aluminum amalgam,[175, 176] sodium and alcohol,[177, 178, 179] and with zinc dust in acetic acid.[180] Furfural phenylhydrazone has been reduced by the following reagents: sodium and alcohol,[179] amalgamated sodium,[181] aluminum and magnesium,[180] a lead cathode in methanolic sulfuric acid.[180] Furonitrile is reduced to the amine by the action of zinc dust in sulfuric acid.[182, 183] Additionally, a mixture of mono-, di-, and trifurfurylamines has been obtained, in low yield, by placing furfuryl bromide in reaction with ammonia in absolute alcohol.[184]

Furfurylamine: $C_4H_3O—CH_2NH_2$; b.p. 49–50° (10 mm.), 145–146° (761 mm.); d_{20}^{20} 1.0570; n_D^{20} 1.4908; **picrate,** m.p. 178–180°; **hydrogen maleate,** m.p. 114°. It is a colorless liquid, turning yellow on standing, and is completely miscible with water. In addition to the references given in the text, see Williams,[185] Winans and Adkins,[186] Adkins and Wojcik,[187] Goodyear Tire and Rubber Company,[188] Paul,[189] Winans,[190]

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[171] Winans, *J. Am. Chem. Soc.*, **61,** 3566 (1939).
[172] Goldschmidt, *Ber.*, **20,** 728 (1887).
[173] Frankland and Ormerod, *J. Chem. Soc.*, **83,** 1342 (1903).
[174] Takaki and Ueda, *J. Pharm. Soc. Japan*, **58,** 276 (1938); *C. A.*, **32,** 5376 (1938).
[175] Tseng and Chang, *Science Repts. Natl. Univ. Peking*, **1,** 19 (1936); *C. A.*, **31,** 05 (1937).
[176] Cinneide, *Proc. Roy. Irish Acad.*, **49, B,** 143 (1943).
[177] Zenoni, *Gazz. chim. ital.*, **20,** 513 (1890).
[178] Gilman and Hewlett, *Iowa State Coll. J. Sci.*, **4,** 27 (1929).
[179] Williams, *Compt. rend. acad. sci. U. S. S. R.*, **1930, A,** 523; *C. A.*, **25,** 5163 (1931).
[180] Wilson, C. L., unpublished work.
[181] Tafel, *Ber.*, **20,** 398 (1887).
[182] Ciamician and Dennstedt, *Ber.*, **14,** 1058, 1475 (1881).
[183] Wallach, *Ann.*, **214,** 193 (1882).
[184] Zanetti and Beckmann, *J. Am. Chem. Soc.*, **50,** 2031 (1928).
[185] Williams, *Ber.*, **60,** 2509 (1927).
[186] Winans and Adkins, *J. Am. Chem. Soc.*, **55,** 2051 (1933).
[187] Adkins and Wojcik, *J. Am. Chem. Soc.*, **56,** 247 (1934).
[188] The Goodyear Tire and Rubber Co., Brit. Pat. 412,914 (1934); *C. A.*, **28,** 7261 (1934).
[189] Paul, *Bull. soc. chim.* [5], **4,** 1121 (1937).
[190] Winans (to Wingfoot Corp.), U. S. Pat. 2,109,159 (1938); *C. A.*, **32,** 2955 (1938).

Sly,[191] Schwoegler and Adkins,[192] Robinson and Snyder,[193] Huber,[194] McNally, Dickey and Gray,[195] Stengel and O'Loughlin.[196] The amine takes up carbon dioxide readily, forming a crystalline mass, m.p. 75°, from which the gas is regenerated on heating.[181] For the crystalline structure of furfurylamine, see Wells.[197]

With ethyl D-tartrate there is produced N,N′-difurfuryltartaramide, $(C_4H_3O—CH_2NH—CO—CHOH—)_2$, m.p. 179°; $[\alpha]_D^{20}$ +97.3°.[173] Related N-furfuryl derivatives of a variety of carboxamides are reported to be useful as softeners and lubricants for conditioning textile yarns.[198] Compounds derived from furfurylamines and dithiocarbamic acid and its derivatives are said to be applicable as accelerators for the vulcanization of rubber.[199, 200]

Attempts to convert the amine to pyridine by passing the vapors over typical dehydrating catalysts at elevated temperatures were unsuccessful.[43] However, catalytic hydrogenation in the liquid phase over Raney nickel gave rise to N-tetrahydrofurfurylpiperidine (43 per cent yield) and piperidine (9 per cent), reaction proceeding by way of the intermediate tetrahydrofurfurylamine.[201]

With ethyl chloroformate in the presence of alkali, the amine is transformed into furfurylurethan, $C_4H_3O—CH_2NH—COOEt$, b.p. 240°[202]; sodium chloroacetate gives rise to N-furfurylglycine, $C_4H_3O—CH_2NHCH_2COOH$, m.p. 210–212°, which is also obtainable, as the ethyl ester (b.p. 99–101° (3 mm.); d_{20}^{25} 1.096; n_D^{25} 1.4735), by condensing furfuryl bromide with ethyl aminoacetate.[203, 204] In the latter synthesis some of the difurfurylated ester is formed simultaneously, and this may be hydrolyzed to N,N-difurfurylglycine, $(C_4H_3O—CH_2)NCH_2COOH$, m.p. 140–141°.[2]

Similarly, furfurylamine and phosgene condense under the influence of potassium hydroxide with formation of *sym*-difurfurylurea, $(C_4H_3O—CH_2NH)_2CO$, m.p. 128°.[202] What may have been the mono-substituted product, furfurylurea (m.p. 105°) was obtained by Gilman and Hewlett[178] by the action of potassium cyanate on furfurylammonium chloride according to the method of Berlinerblau.

2-(N-nitrosofurfurylamino)isobutyl methyl ketone, $C_4H_3O—CH_2N(NO)C(CH_3)_2CH_2COCH_3$, b.p. 158° (0.8 mm.) is obtained in 40 per cent yield by the action of nitrous acid on an equimolecular mixture of furfurylamine and mesityl oxide. It undergoes alkaline decomposition to give 2-(diazomethyl)furan in 12 per cent yield.[2]

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[191] Sly (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,112,715 (1938); *C. A.*, **32** 3767 (1938).

[192] Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).

[193] Robinson and Snyder, "Organic Syntheses," **23**, 68, New York, John Wiley and Sons (1943).

[194] Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).

[195] McNally, Dickey and Gray (to Eastman Kodak Co.), U. S. Pat. 2,338,655 (1944); *C. A.*, **38**, 3672 (1944).

[196] Stengel and O'Loughlin (to Commercial Solvents Corp.), U. S. Pat. 2,315,13[illegible] (1943); *C. A.*, **37**, 5419 (1943).

[197] Wells, *Phil. Mag.*, **37**, 184 (1946); *C. A.*, **41**, 2955 (1947).

[198] Dickey and McNally (to Eastman Kodak Co.), U. S. Pat. 2,388,833 (1945); *C. A.*, **40**, 743 (1946).

[199] Cramer (to Wingfoot Corp.), U. S. Pat. 2,150,423 (1939); *C. A.*, **33**, 5230 (1939).

[200] Cramer (to Wingfoot Corp.), U. S. Pat. 2,150,424 (1939); *C. A.*, **33**, 5232 (1939).

[201] Wilson, *J. Am. Chem. Soc.*, **67**, 693 (1945).

[202] Marckwald *Ber.*, **23**, 3207 (1890).

[203] Dahlen (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,098,861 (1937); *C. A.*, **32**, 367 (1938).

[204] Zanetti and Bashour, *J. Am. Chem. Soc.*, **62**, 1511 (1940).

[205] Adamson and Kenner, *J. Chem. Soc.*, **1935**, 286.

For the transformation of the amine into N-furfuryl-N-methylacetamidine, b.p. 94° (1 mm.); picrate, m.p. 92.5–93°, see Oxley and Short.[206]

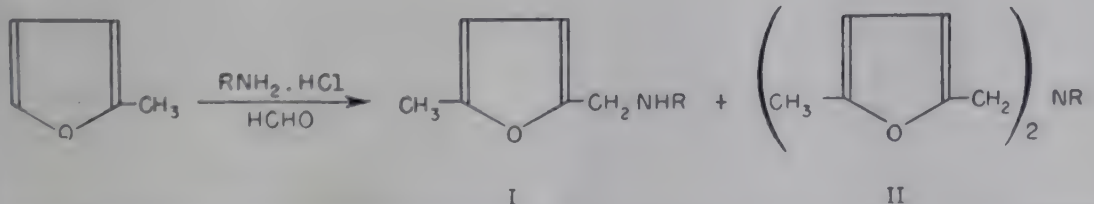
When furfurylamine is dry distilled with saccharic acid under reduced pressure, N-furfurylpyrrole, b.p. 76–78° (0.2 mm.) is obtained in 50 per cent yield. From the product there was obtained N-furfurylpyrrole-2-carbonal, b.p. *ca.* 100° (2 mm.); semicarbazone, m.p. 175.5°, and the corresponding carboxylic acid, m.p. 120–122°.[207, 3]

Difurfurylamine: $(C_4H_3O—CH_2)_2NH$; b.p. 102–103° (1 mm.); 126–128° (10 mm.); **hydrochloride,** m.p. 186–187°; **picrate,** m.p. 123–125°[184, 186, 188, 189, 190, 171, 194, 195] (see also [185]).

Trifurfurylamine: $(C_4H_3O—CH_2)_3N$; b.p. 136–138° (1 mm.); **hydrochloride,** m.p. 156–157°; **picrate,** m.p. 132°. Obtained in 38 per cent yield by hydrogenation of hydrofuramide over Adams platinum oxide catalyst in ethanolic acetic acid[208] (see also [184]).

Mixed Furfurylamines:

The secondary amines of this classification are listed in Table 5. For the most part, those related to furfuryl alcohol were synthesized (a) from the corresponding 2-furaldimines by reduction with sodium and alcohol, or catalytically with hydrogen over Raney nickel, and (b) by furfurylation of primary amines with furfuryl bromide. Presumably they might also be obtained by aminomethylation of furan; by condensation of the latter with formaldehyde and a primary amine salt (the Mannich reaction). Little is known about this reaction as applied to furan, and it must be admitted that failure attended an effort to effect a related condensation involving a secondary amine. Thus, furan, formaldehyde, and dimethylamine in aqueous acetic acid did not produce the expected tertiary amine, N,N-dimethylfurfurylamine.[78] Possibly the use of a stronger acid (hydrochloric acid) would have permitted the reaction to go forward, since the mobility of the nuclear hydrogen atoms should be promoted by an increase in the hydrogen ion concentration. In any event, Mannich bases are obtainable from the more reactive 2-methylfuran in the presence of either acid.[209, 78] In this way, condensation with primary amine salts and formaldehyde gives rise to secondary amines, I (see Table 5), related to 5-methylfurfuryl alcohol, and in addition, the corresponding N,N-bis(5-methylfurfuryl)alkylamines, II (see Table 6).



I II

[206] Oxley and Short, *J. Chem. Soc.*, **1948**, 1514.
[207] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).
[208] Gilman and Dickey, *Iowa State Coll. J. Sci.*, **5**, 193 (1931).
[209] Holdren and Hixon, *J. Am. Chem. Soc.*, **68**, 1198 (1946).

Table 5. Some Furfuryl Secondary Amines

Amines Related to Furfuryl Alcohol

Type:  CH_2NHR

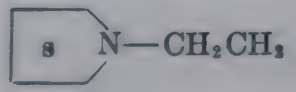
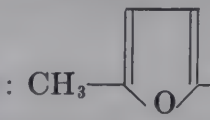
N—R—furfurylamine: R	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
CH_3	b.p. 149–149.5 (761 mm.) d_{25}^{25} 0.992 n_D^{20} 1.4729	hydrochloride, 144–146 hydrogen maleate, 172–173	210, 211, 212; see also 150, 213
C_2H_5	b.p. 165–167 (761 mm.) d_{25}^{25} 0.963 n_D^{20} 1.4688	hydrochloride, 127–128, 130–131 picrate, 116	210, 214, 215
	b.p. 94–97 (0.30 mm.)	hydrochloride (bis), 212	216
n-C_3H_7	b.p. 80–81 (20 mm.) d_{25}^{25} 0.947 n_D^{20} 1.4679	hydrochloride, 138–140	217
n-C_4H_9	b.p. 198–200 (768 mm.) d_{25}^{25} 0.935 n_D^{20} 1.4669	hydrochloride, 189–191	210, 218
$(CH_3)_2C(NO_2)CH_2$	b.p. 97–98 (0.6 mm.)	—	219
n-C_5H_{11}	b.p. 214–216 (756 mm.) d_{25}^{25} 0.927 n_D^{20} 1.4668	hydrochloride, 185–188	210
$C_6H_5CH_2$	b.p. 115–124 (4 mm.), 118–120 (2 mm.) n_D^{20} 1.5543–1.5580	hydrochloride, 208–212 (dec.) phenylthiourea, 80–81 N-benzoyl, 71–72	220, 218

TABLE 5 (*Continued*)

N—R—furfurylamine: R	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
C_6H_5	b.p. 109–110 (0.5 mm.), 146–148 (10 mm.) d_{20}^{20} 1.119, d_{25}^{25} 1.110 n_D^{20} 1.5834	hydrochloride, 150–151 (dec.)	210, 221, 78; see also 222
p-HOC_6H_4	m.p. 108–110, 110–111	—	218, 223, 224
2-$C_{10}H_7$	b.p. 162–168 (42–45 mm.)	hydrochloride, 172	225, 226, 227
2-C_5H_4N	b.p. 118–119 (1.5 mm.)	hydrochloride, 164–166 picrate, 164.8–165.8	228, 216

TABLE 5 (*Continued*)

Amines Related to 5-Methylfurfuryl Alcohol

Type:  CH_2NHR

N-(5-methylfurfuryl)alkylamine: R	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
C_2H_5	b.p. 71–76 (17 mm.) d_4^{25} 0.944 n_D^{25} 1.4689	hydrochloride, 138–139	209
$HOCH_2CH_2$	b.p. 100–102 (3 mm.) d_4^{25} 1.082 n^{25} 1.5020	hydrochloride, 79–79.5	209
i-C_3H_7	b.p. 82–83 (20 mm.) d_4^{25} 0.923 n^{25} 1.4630	hydrochloride, 138–139	209
CH_2=$CHCH_2$	b.p. 93 (21 mm.) d_4^{25} 0.959 n^{25} 1.4832	hydrochloride, 90–91	209
n-C_4H_9	b.p. 110–115 (22 mm.) d_4^{25} 0.921 n^{25} 1.4659	hydrochloride, 169–170	209
$CH_3(CH_2)_7$	b.p. 115–118 (2 mm.) d_4^{25} 0.901 n^{25} 1.4671	hydrochloride, 145–146	209

$CH_3(CH_2)_{11}$	b.p. 135 (2 mm.) d_4^{25} 0.888 n^{25} 1.4678	hydrochloride, 147–148	209
$CH_3(CH_2)_{17}$	b.p. 195–197 (2 mm.) m.p. 27–28	hydrochloride, 105–107	209
C_6H_{11}	b.p. 75–77 (1 mm.) d_4^{25} 0.984 n^{25} 1.4960	hydrochloride, 167–168	209
$C_6H_5CH_2$	b.p. 104–108 (1 mm.) d_4^{25} 1.042 n^{25} 1.5411	hydrochloride, 178–180 (dec.)	209

Miscellaneous Secondary Amines

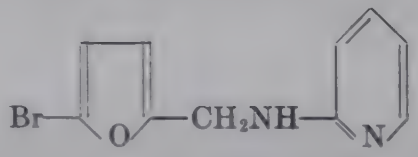
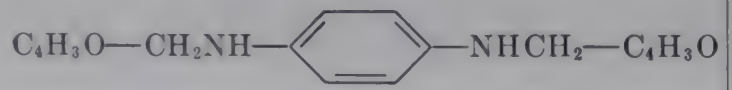
Structure			
	b.p. 159–161 (5 mm.) m.p. 61	—	228
	b.p. 134–137 (0.6 mm.) m.p. 72	—	228
	m.p. 75–77	—	218
	m.p. 155.5–156	—	218

TABLE 6. SOME FURFURYL TERTIARY AMINES

Amines Related to Furfuryl Alcohol

Type:  $-CH_2NRR'$

N-R-N-R′-furfurylamine:		Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
R	R′			
CH_3	CH_3	b.p. 142–145 (atm.) n_D^{25} 1.4609	picrate, 102–103 methiodide, 116–117, 119 ethiodide, 102.5, 103–104 [other quaternary ammonium compounds, alkyl (C_3–C_{18}) dimethylfurfurylammonium iodides, are described by Fellows and Livingston (229) and by Weilmuenster and Jordan(230)]	229, 230, 78; see also 211, 231, 178
CH_3	C_2H_5	b.p. 69–70 (23 mm.)	picrate, 91 methiodide, 101 furfuryl bromide, 151	150
C_2H_5	C_2H_5	b.p. 169–172 (atm.)	picrate, 84–85 methiodide, 124–125 ethiodide, 137 (other quaternary salts described)	230
CH_3	$HOCH_2CH_2$	b.p. 105 (6 mm.)	picrate, 68–70 methiodide, 77–80	150
C_2H_5	$HOCH_2CH_2$	b.p. *ca.* 127 (12 mm.)	picrolonate, 159	215
CH_3	C_6H_{11}—CH_2	b.p. 103–105 (5 mm.)	hydrochloride, 107–108	232
CH_3	C_6H_{11}—CH_2CH_2	b.p. 121–123 (5 mm.)	hydrochloride, 163–164	232

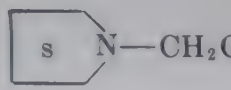
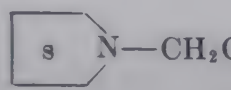
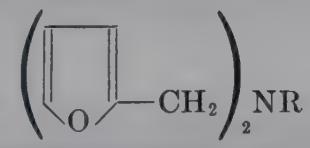
$(CH_3)_2C(NO_2)CH_2$	C_6H_{11}	b.p. 153–155 (0.1 mm.) d_{20}^{20} 1.0775 n_D^{20} 1.5010	—	233, 219
$(CH_3)_2C(NH_2)CH_2$	C_6H_{11}	b.p. 142–143 (5 mm.) d_{20}^{20} 0.9892 n_D^{20} 1.4983	—	233, 219
C_2H_5	p-ClC_6H_4—$CH(OH)CH_2$	b.p. 176 (10 mm.) n_D^{20} 1.5423	—	234
CH_3	C_6H_5—CH_2	b.p. 131–133 (13 mm.)	methiodide, 135 benzyl bromide, 167	231
CH_3	C_4H_3S—CH_2	b.p. 132–135 (14 mm.)	picrate, 78 methiodide, 110	231
CH_3	C_6H_5	b.p. 142–145 (10 mm.) n_D^{20} 1.5760	—	78
C_2H_5	C_6H_5	b.p. 134–134.5 (5 mm.) d_{20}^{20} 1.0694, d_0^{20} 1.0670	p-nitroso, 75–76	221
$HOCH_2CH_2$	C_6H_5—CH_2	b.p. 122–126 (0.08 mm.) n_D^{20} 1.5481	hydrochloride, 152–154 (dec.)	220
$ClCH_2CH_2$	C_6H_5—CH_2	—	hydrochloride, 118–120 (dec.)	220
$(CH_3)_2NCH_2CH_2$	C_6H_5	—	bishydrochloride, 134	235, 236
$(CH_3)_2NCH_2CH_2$	p-$(CH_3O)C_6H_4$	b.p. 137–139 (0.030 mm.)	hydrochloride (mono), 125–126 bisuccinate, 96–97	237
$(CH_3)_2NCH_2CH_2$	2-C_5H_4N	b.p. 117.5–118 (0.2 mm.), 136–137 (0.7 mm.) n_D^{20} 1.5486	hydrochloride (mono), 117–119 dihydrogen citrate, 95–97 fumarate, 142	238, 152, 228; see also 236, 239
	2-C_5H_4N	b.p. 149–153 (0.25 mm.)	citrate, 133–138	216
		b.p. 188 (1.6 mm.)	citrate, 135–136	216

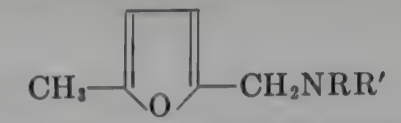
TABLE 6. *Continued*

Type: 

N-R-difurfurylamine: R	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
CH_3	b.p. 100–102 (5 mm.), 237–238 (—) d_{25}^{25} 1.074 n_D^{20} 1.5086	hydrochloride, 153–154	217, 211
C_2H_5	b.p. 109–110 (5 mm.) d_{25}^{25} 1.055 n_D^{20} 1.5059	hydrochloride, 149–151	217
C_3H_7	b.p. 115–117 (5 mm.) d_{25}^{25} 1.034 n_D^{20} 1.4978	hydrochloride, 147–148	217
C_4H_9	b.p. 126–128 (5 mm.) d_{25}^{25} 1.019 n_D^{20} 1.4976	hydrochloride, 105–106	217
C_5H_{11}	b.p. 137–139 (5 mm.) d_{25}^{25} 1.005 n_D^{20} 1.4950	hydrochloride, 103–105	217
C_6H_5	b.p. 163–167 (5 mm.) m.p. 31–32	hydrochloride, 137–141	217

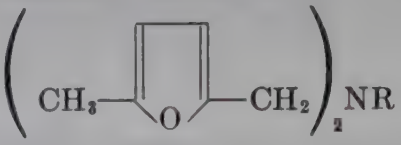
TABLE 6. *Continued*

Amines Related to 5-Methylfurfuryl Alcohol

Type: 

N-R-N-R′-5-methylfurfurylamine:		Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
R	R′			
CH_3	CH_3	b.p. 68–70 (25 mm.), 161–164 (—) d_4^{25} 0.921 n^{25} 1.4620	hydrochloride, 158–158.5, 160.5–161 picrate, 116–116.5 methiodide, 161–162 (dec.)	209, 78

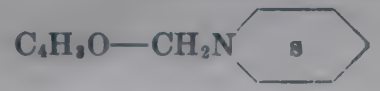
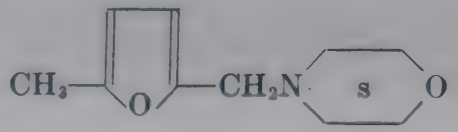
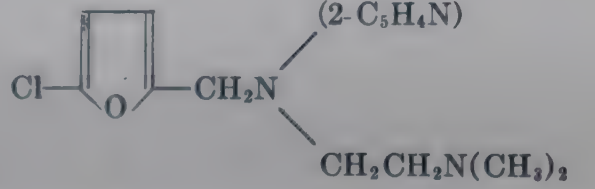
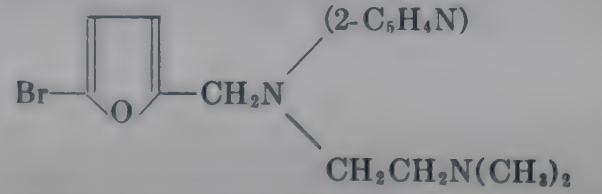
TABLE 6. *Continued*

Type: 

N,N-bis(5-methylfurfuryl)alkylamine:	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
R			
C_2H_5	b.p. 127–130 (6 mm.) d_4^{25} 1.018 n^{25} 1.5000	hydrochloride, 151–152	209
$CH_3(CH_2)_7$	b.p. 150–153 (1 mm.) d_4^{25} 0.947 n^{25} 1.4840	acid oxalate, 202–203 (dec.)	209
$C_6H_5CH_2$	b.p. 138–141 (1 mm.) d_4^{25} 1.069 n^{25} 1.5440	hydrochloride, 154–156 (dec.)	209

TABLE 6. *Continued*

Miscellaneous Tertiary Amines

Structure	Physical constants (°C.)	Derivatives, m.p. (°C)	Ref.
	b.p. 93–94 (11 mm.)	picrate, 107–108 methiodide, 172.5–173.5	218, 78
	b.p. 88–89 (6 mm.), 105–107 (11 mm.) d_4^{25} 0.981 n^{25} 1.4950	hydrochloride, 146.5–147.5	209, 78
	b.p. 133 (20 mm.) d_4^{25} 1.057 n^{25} 1.4961	hydrochloride, 202–204 (dec.)	209
	b.p. 149–152 (2 mm.)	fumarate, 109	228
	b.p. 135–140 (0.4 mm.), 156–158 (0.5 mm.)	fumarate, 136	228, 238

The known tertiary amines (Table 6) containing a furfuryl radical have been obtained by more or less standard procedures involving alkylation of the appropriate secondary amines with alkyl or furfuryl halides, in the presence of suitable condensing agents. Additionally, the lower N,N-dialkylfurfurylamines have been prepared by the Leuckart synthesis, whereby furfural is condensed with N,N-dialkylformamide[230] (see also [78, 211]).

A number of these amines have been tested for their pharmacological activity.[228, 216, 237, 238, 232, 234, 240] Among others, the furan analog of Pyribenzamine, N-β-dimethylaminoethyl-N-2-pyridylfurfurylamine, and the corresponding 5-halofurfuryl compounds, have been found to be potent antihistaminics.[241] N-β-chloroethyl-N-benzylfurfurylamine, III, which is related to the sympatholytic drug, Dibenamine, was synthesized by Campbell[222] by condensing N-benzylfurfurylamine with ethylene oxide (see also

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[210] Zanetti and Bashour, *J. Am. Chem. Soc.*, **61**, 3133 (1939).

[211] Nabenhauer (to Smith, Kline and French Laboratories), U. S. Pat. 2,185,219 (1940); *C. A.*, **34**, 3023 (1940).

[212] Herz, *J. Am. Chem. Soc.*, **67**, 2272 (1945).

[213] Schwabbauer, *Ber.*, **35**, 410 (1902).

[214] Lutz *et al.*, *J. Org. Chem.*, **12**, 760 (1947).

[215] Braun and Braunsdorf, *Ber.*, **54**, 2081 (1921).

[216] Lincoln, Heinzelmann and Hunter, *J. Am. Chem. Soc.*, **71**, 2902 (1949).

[217] Zanetti and Bashour, *J. Am. Chem. Soc.*, **62**, 742 (1940).

[218] Adkins and Winans, U. S. Pat. 2,175,585 (1939); *C. A.*, **34**, 779 (1940).

[219] Senkus (to Commercial Solvents Corp.), U. S. Pat. 2,465,958 (1949); *C. A.*, **43**, 5424 (1949).

[220] Campbell, Ackerman and Campbell, *J. Am. Chem. Soc.*, **71**, 2905 (1949).

[221] Umnova, *J. Gen. Chem. U. S. S. R.*, **10**, 569 (1940); *C. A.*, **34**, 7902 (1940).

[222] Schiff, *Ber.*, **19**, 2153 (1886).

[223] Winans, Brit. Pat. 497,778 (1938); *C. A.*, **33**, 4078 (1939).

[224] Bean (to Eastman Kodak Co.), U. S. Pat. 2,241,760 (1941); *C. A.*, **35**, 5131(1941).

[225] Musajo and Pepe, *Gazz. chim. ital.*, **61**, 910 (1931); *C. A.*, **26**, 2737 (1931).

[226] Musajo, *Gazz. chim. ital.*, **60**, 673 (1930); *C. A.*, **25**, 955 (1931).

[227] Lauter (to Wingfoot Corp.), U. S. Pat. 2,028,047 (1936).

[228] Hayes, Gever and Orcutt, *J. Am. Chem. Soc.*, **72**, 1205 (1950).

[229] Fellows and Livingston, *J. Pharmacol. Exptl. Therap.*, **68**, 231 (1940).

[229a] Davis, *J. Pharmacol.*, **79**, 37 (1943).

[229b] Boyd and Lapp, *J. Pharmacol.*, **87**, 24 (1946).

[230] Weilmuenster and Jordan, *J. Am. Chem. Soc.*, **67**, 415 (1945).

[231] Braun, Fussgänger and Kühn, *Ann.*, **445**, 222 (1925).

[232] Blicke and Zienty, *J. Am. Chem. Soc.*, **61**, 771 (1939).

[233] Senkus, *J. Am. Chem. Soc.*, **72**, 2069 (1950).

[234] Lutz *et al.*, *J. Org. Chem.*, **12**, 617 (1947).

[235] Gaillot, Rouze, and Gastou (to Société des usines chimiques Rhône-Poulenc), U. S. Pat. 2,526,943 (1950).

[236] Société des usine chimiques Rhône-Poulenc, Brit. Pat. 605,710 (1948); *C. A.*, **43**, 822 (1949).

[237] Biel, *J. Am. Chem. Soc.*, **71**, 1306 (1949).

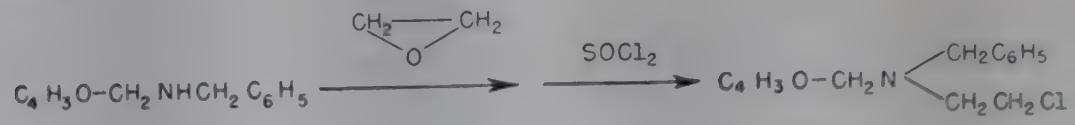
[238] Vaughan and Anderson, *J. Am. Chem. Soc.*, **70**, 2607 (1948).

[239] Viaud, *Technologie Produits Pharmaceutiques*, **2**, 53 (1947); *Drug Trade News*, **22**, (9) 63 (1947).

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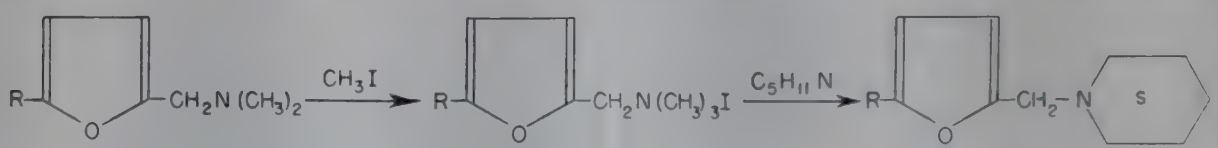
[241] Orcutt and Prytherch, *J. Pharmacol. Exptl. Therap.*, **99**, 479 (1950).

150, 217) and subsequently treating the resulting amino alcohol with thionyl chloride.



III

The tertiary amines readily combine with alkyl halides to form the corresponding quaternary ammonium compounds.[213, 230] Several of these types, derived from N,N-dimethylfurfurylamine, IV (R = H), have been found to cause complex and variable vascular action[229] (see also [229a, 229b]). The methiodide, V (R = H) the so-called Furmethide, is reported to be useful medicinally for the treatment of urinary retention due to bladder atony.[229] When heated with piperidine, V (R = H) and its homolog (V, R = CH_3), have been shown to undergo an exchange reaction to form N-furfurylpiperidine, VI (R = H) and the corresponding 5-methyl compound,[k] VI (R = CH_3), respectively.[78] Interestingly enough, the hydrochlorides of IV (R = H or CH_3) do not permit such an exchange.[78] At elevated



IV V VI

temperature (> 180°), furfuryltrimethylammonium iodide (V, R = H; VA) reacts with sodium cyanide to give, as the major product, furylacetonitrile, VII.[78] In lesser amount there is formed the product of allylic reaction, 5-methyl-2-furonitrile, VIII, hence the behavior of the quaternary salt is related to that of furfuryl halides (p. 550), and the difference in the relative proportions of "normal" and "abnormal" products may be due to the widely varying experimental conditions employed. Similar treatment of V (R = CH_3) gave rise to the "normal" product, 5-methyl-2-furylacetonitrile in 37 per cent yield.[78]



VA VII VIII

Sulfur Derivatives. *Furfuryl Mercaptan and Related Compounds.* Furfuryl mercaptan is a colorless, relatively stable, liquid product, the physical properties of which have been reported as follows: b.p. 45–47° (12 mm.), 84° (65 mm.), 155° (atm.); d_{20}^{20} 1.1339, d_4^{20} 1.1319; n_D^{20} 1.5329. It is insoluble

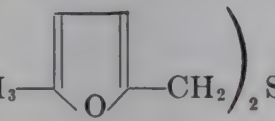
[k] VI (R = CH_3) is also obtainable from 2-methylfuran by the Mannich reaction using formaldehyde and piperidine in hydrochloric[209] or acetic acids[78]. The related N-5-methylfurfurylmorpholine was prepared in a similar manner[209].

in water; soluble in organic solvents, and in aqueous alkali. Useful identifying derivatives are the *p*-nitrobenzoate, m.p. 76–77°,[242, 243] and the thioether, furfuryl 2,4-dinitrophenyl sulfide, m.p. 130°.[244] The mercaptan possesses a very intense, disagreeable odor, but at very low concentration (1 p.p.m.), in a suitable solvent, the odor is strongly suggestive of the aroma of roasted coffee, and it has been suggested for inclusion in artificial coffee oil.[245] Actually, it has been isolated as a component of the oil derived from roasted coffee.[3, 5]

Preparation is accomplished from furfural by way of furfuryl disulfide,[1] I, which is subsequently reduced to the mercaptan. The first step involves treatment of the aldehyde, in alcohol, with ammonium hydrosulfide, or with sodium sulfide and hydrogen sulfide.[242, 246, 247, 248, 243] The disulfide so formed may be isolated, or reduced directly by zinc and acetic acid, or by activated aluminum or amalgamated aluminum in alcohol. The yield of mercaptan is quite high; 70–90 per cent based on the original furfural. It has also been obtained[166] by hydrolysis, without isolation, of the product (presumably S-furfurylisothiourea; see below) obtained by condensation of furfuryl chloride with thiourea.

$$C_4H_3O{-}CHO \xrightarrow{NaSH} \underset{I}{C_4H_3O{-}CH_2S{-}SCH_2{-}C_4H_3O} \xrightarrow{(H)} C_4H_3O{-}CH_2SH$$

Furfuryl disulfide: I; m.p. 10–10.5°; b.p. 112–115° (0.5 mm.), 160–165° (5 mm.; some decomposition). It is soluble in most organic solvents, and while the odor is not very strong, it is tenacious and unpleasant.[242, 249, 248, 243]

5-Methylfurfuryl disulfide:  m.p. 42°; b.p. *ca.* 150° (0.5 mm.).

Prepared from 5-methylfurfural by treatment with ammonium hydrosulfide in ethanol.[250, 247, 251]

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[1] In all probability, the disulfide, I, has its origin in preliminarily formed polythiofurfural which is reduced to I during the heating period with sulfide.

[242] Staudinger and Reichstein (to Internationale Nahrungs- und Genussmittel A.-G.), U. S. Pat. 1,715,795 (1929); *C. A.*, **23**, 3715–3716 (1929).

[243] Gilman and Hewlett, *J. Am. Chem. Soc.*, **52**, 2141 (1930).

[244] Bost, Turner and Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1923).

[245] Cargille Scientific Inc., *Chem. Eng. News*, **27**, 940 (1949).

[246] Staudinger and Reichstein (to Internationale Nahrungs- und Genussmittel A.-G.), Canadian Pat. 283,765 (1928); *C. A.*, **22**, 4537 (1928).

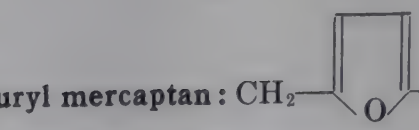
[247] Internationale Nahrungs- und Genussmittel A.-G., Brit. Pat. 286,152 (1927), *C. A.*, **23**, 155 (1929).

[248] Staudinger and Reichstein (to Internationale Nahrungs- und Genussmittel A.-G.), German Pat. 484,244 (1926); *C. A.*, **24**, 965 (1930).

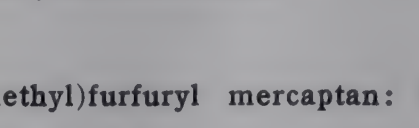
[249] Internationale Nahrungs- und Genussmittel, A.-G., Swiss Pat. 136,378 (1927); *C. A.*, **24**, 4358 (1930).

[250] Staudinger and Reichstein (to Internationale Nahrungs- und Genussmittel, A.-G.), German Pat. 485,138 (1927); *C. A.*, **24**, 865 (1930).

[251] Kipnis, Levy and Ornfelt, *J. Am. Chem. Soc.*, **71**, 2270 (1949).

5-Methylfurfuryl mercaptan:  ; b.p. 61–62° (13 mm.), 70° (3 mm.); n_D^{20} 1.5258; **p-nitrobenzoate,** m.p. 82–83°; by reduction of the preceding disulfide with zinc in acetic acid[250, 247] or with aluminum amalgam.[251]

5-(Hydroxymethyl)furfuryl disulfide:  ; m.p. 136–137°; from 5-(hydroxymethyl)furfural and ammonium or sodium hydrosulfide.[252, 250, 247] The corresponding methoxymethyl compound, m.p. 36–37°, was similarly derived from 5-(methoxymethyl)furfural.[247]

5-(Hydroxymethyl)furfuryl mercaptan:  ; b.p. 106–109° (2 mm.), 115–118° (0.5 mm.); by reduction of the disulfide.[252, 250, 247] The methoxymethyl mercaptan, b.p. 78–80° (—).[247]

S-furfurylisothiourea: $C_4H_3O—CH_2S—C(NH)NH_2$; obtained, as the **hydrochloride,** m.p. 142–143°, on refluxing furfuryl chloride with thiourea in acetone. **Picrate,** m.p. 162°.[168] The hydrochloride failed to give furylmethanesulfonyl chloride when subjected to the action of aqueous chlorine.

Gilman and Hewlett[253] observed that furfuryl mercaptan polymerizes slowly on standing (sealed tube conditions); that after about one year it is highly viscous and contains, in suspension, a white, odorless solid, m.p. 135°, having the same composition as the original mercaptan. Distillation, under reduced pressure, regenerated the mercaptan in 33 per cent yield.

Below are listed the known sulfides, derived from furfuryl mercaptan or from furfuryl chloride by appropriate reactions.

Sulfides (thioethers):

Furfuryl ethyl sulfide: $C_4H_3O—CH_2SC_2H_5$; b.p. 90.5–91° (28 mm.); d_{20}^{20} 1.0514; d_4^{20} 1.0496; n_D^{20} 1.5140. Prepared by treating sodium furfuryl sulfide with ethyl bromide.[166]

Furfuryl 2-chloroethyl sulfide: $C_4H_3O—CH_2SCH_2CH_2Cl$; b.p. 128° (5 mm.); d_{30}^{30} 1.1914; n_D^{30} 1.5200. Obtained in 90 per cent yield by successive treatment of furfuryl mercaptan with ethylmagnesium bromide and 2-chloroethyl *p*-toluenesulfonate. It has decided vesicant properties whereas the homolog immediately following produces no skin irritation.[243]

Furfuryl 3-chloropropyl sulfide: $C_4H_3O—CH_2SCH_2CH_2CH_2Cl$; b.p. 135° (5 mm.); d_{30}^{30} 1.1687; n_D^{25} 1.4740; in 79 per cent yield as in the preceding synthesis, but using 3-chloropropyl *p*-toluenesulfonate.[243]

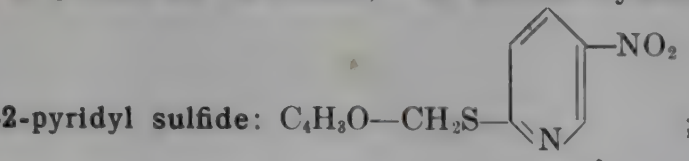
Furfuryl 2-diethylaminoethyl sulfide: $C_4H_3O—CH_2SCH_2CH_2N(C_2H_5)_2$; b.p. 117° (3 mm.); from sodium furfuryl sulfide and 2-diethylaminoethyl chloride.[169]

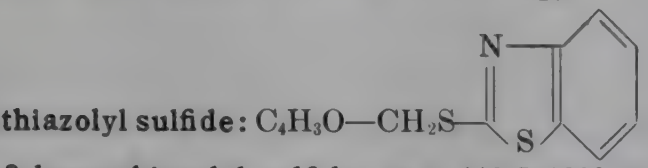
Furfuryl phenyl sulfide: $C_4H_3O—CH_2SC_6H_5$; b.p. 106–108° (2 mm.); from furfuryl chloride and sodium phenyl sulfide.[169]

Furfuryl 2,4-dinitrophenyl sulfide: $C_4H_3O—CH_2S—C_6H_3(NO_2)_2$; m.p. 127.5–128°,

[252] Staudinger and Reichstein (to Internationale Nahrungs- und Genussmittel A.-G.), U. S. Pat. 1,748,527 (1930); *C. A.*, **24,** 1869 (1930).

130°. Obtained from furfuryl mercaptan by the action of 2,4-dinitrochlorobenzene in the presence of potassium carbonate,[169] or sodium hydroxide.[244]

Furfuryl 5-nitro-2-pyridyl sulfide:  ; m.p. 114°.[169]

Furfuryl 2-benzothiazolyl sulfide:  ; b.p. 205–207° (7 mm.)[169]

Furfuryl 6-nitro-2-benzothiazolyl sulfide: m.p. 119.5–120°.[169]

Homologous 2-Furylalkanols

The compounds described here are divided into two major classifications, (a) homologs of furfuryl alcohol which possess no nuclear substituent other than the group containing the hydroxyl (the lateral homologs), and (b) homologs which additionally possess one or more hydrocarbon radicals attached to the nucleus (the nuclear homologs).

Lateral Homologs

Primary Alcohols and Their Derivatives.

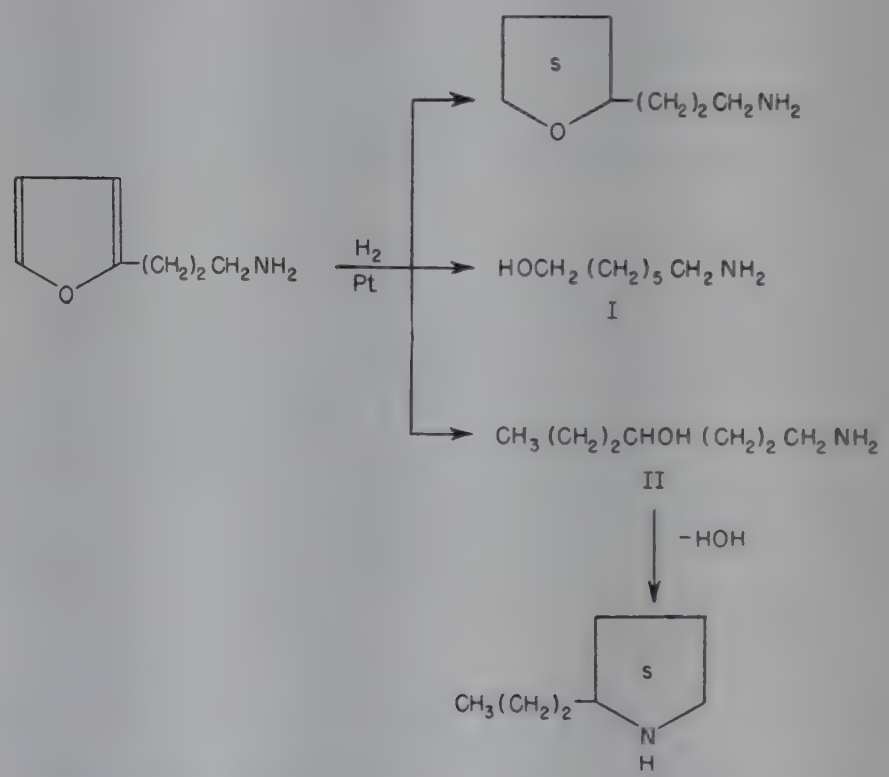
2-(2-Furyl)ethyl alcohol: $C_4H_3O—CH_2CH_2OH$; b.p. 86–88° (21 mm.); n_D^{25} 1.4788; d_4^{25} 1.0705; **α-naphthylurethan,** m.p. 85.2–86°; in 32 per cent yield by Bouveault-Blanc type reduction of 2-furylacetic ester.[165, 254] **Chloride:** b.p. 70–71° (21 mm.); n_D^{25} 1.4788; d_4^{25} 1.1229; in 61 per cent yield from the alcohol by the action of thionyl chloride in ether and pyridine.[165] Treatment with magnesium in ether containing a small amount of iodine produces a stable Grignard reagent, which on carbonation gives rise to the expected 3-(2-furyl)propionic acid.[165] **Amine:** b.p. 155° (752 mm.); n_D^{21} 1.4799; d^{20} 1.0080; oxalate, m.p. 171–172°; picrate m.p. 129°; chloroplatinate, m.p. 183–184°. Prepared (a) from 3-(2-furyl)propionic acid through the corresponding azide (the Curtius reaction),[255] (b) from furylacetaldoxime by reduction with sodium amalgam,[256, 257] (c) by electrolytic reduction of 2-(2-nitrovinyl)furan.[258] For physiological properties, see Windaus and Dalmer.[255] Hydrogenation over a platinum catalyst cleaved the ring with formation of 1-amino-3-hexanol, or 6-amino-1-hexanol, or a mixture of two.[258]

3-(2-Furyl)propyl alcohol: $C_4H_3O—(CH_2)_2CH_2OH$; b.p. 90–91° (4 mm.); n_D^{25} 1.4760; d_{20}^{20} 1.0613; **α-napthylurethan,** m.p. 49°, 57–59°; **acetate,** b.p. 92° (2 mm.); n_D^{25} 1.4553; d_{20}^{20} 1.0601. Prepared by catalytic hydrogenation of 3-(2-furyl)acrolein[259, 260, 261, 262]

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[253] Gilman and Hewlett, *Iowa State Coll. J. Sci.*, **5,** 19 (1930).
[254] Ryan, Plucker and Amstutz, *J. Am. Chem. Soc.*, **62,** 2037 (1940).
[255] Windaus and Dalmer, *Ber.*, **53,** 2304 (1920).
[256] Asahina and Fujita, *J. Pharm. Soc. Japan*, **490,** 1084 (1922); *C. A.*, **17,** 2578 (1933).
[257] Yabuta and Kambe, *Proc. Imp. Acad. Tokyo*, **4,** 120 (1928); *C. A.*, **22,** 4503 (1928).
[258] Takamoto, *J. Pharm. Soc. Japan*, **48,** 136, 366 (1928); *C. A.*, **22,** 2354, 3162 (1928).
[259] Bray and Adams, *J. Am. Chem. Soc.*, **49,** 2101 (1927).
[260] Burdick and Adkins, *J. Am. Chem. Soc.*, **56,** 438 (1934).
[261] Hinz, Meyer and Schücking, *Ber.*, **76,** 676 (1943).
[262] Hofmann, Chen, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **69,** 191 (1947).

(see also [263]). On heating for several hours over alumina at 450°, the alcohol gives rise to a mixture of propylfuran, propenylfuran and furylpropanone.[40] **Chloride**: b.p. 60° (5 mm.); d_{25}^{25} 1.0813; n_D^{25} 1.4730; from the alcohol by the action of thionyl chloride.[158, 164, 264, 265] The chloride resisted attempts to form the corresponding Grignard reagent,[158, 164] but the halogen was readily replaced by the action of aqueous potassium cyanide, hydrolysis of the resulting nitrile producing furylbutyric acid in 60 per cent yield.[264] **Amine**: b.p. 90.5° (15 mm.), 172.5–173° (754 mm.); picrate, m.p. 165–166°; by the action of sodium amalgam on the oxime of 3-(2-furyl)-acrolein,[266, 267] and from 2-cyano-3-(2-furyl)propionic acid on reduction with sodium and butanol.[268] Catalytic hydrogenation over platinum produces tetrahydrofurylpropylamine and aminoheptanol[266] (see also [269]). The latter may be a mixture of the two isomers, I and II, but certainly some II is produced, since under the conditions employed by Šorm and Brandejs,[268] 2-propylpyrrolidine is formed, the anticipated cyclodehydration product of II.



3-(2-Furyl)-2-phenylpropyl alcohol: $C_4H_3O—CH_2CH(C_6H_5)CH_2OH$; no constants; in very low yield by the action of nitrous acid on the corresponding amine.[270] **Amine**: b.p. 282–283° (—); hydrochloride, m.p. 176°; picrate, m.p. 152°. Obtained along with 2-(2-phenylethyl)furan by condensation of furfural with phenylacetonitrile, and reduction of the resulting 2-phenyl-3-(2-furyl)acrylonitrile using sodium and alcohol[270] (see also Woodward[163]).

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[263] Wienhaus and Leonhardi, *Ber. Schimmel & Co., Akt.-Ges.*, **1929**, 225; *C. A.*, **24**, 2127 (1930).

[264] Hofmann, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **71**, 1253 (1949).

[265] Hofmann (to Ciba Pharmaceutical Products, Inc.), U. S. Pat. 2,527,421 (1950).

[266] Takamoto, *J. Pharm. Soc. Japan*, **48**, 686 (1928); *C. A.*, **23**, 387 (1929).

[267] Takamoto and Hirohashi, *J. Pharm. Soc. Japan*, **48**, 446 (1928); *C. A.*, **22**, 3409 (1928).

4-(2-Furyl)butyl alcohol: $C_4H_3O—(CH_2)_3CH_2OH$; b.p. 115–117° (18 mm.); **α-naphthylurethan,** m.p. 71–73°. Prepared by Bouveault-Blanc type reduction of furylbutyric ester.[264, 265]

5-(2-Furyl)pentyl alcohol: $C_4H_3O—(CH_2)_4CH_2OH$; b.p. 125–130° (16 mm.); **α-naphthylurethan,** m.p. 58–58.5°; from furylvaleric ester as in preceding preparation.[271, 272, 265, 273]

Secondary Alcohols and Their Derivatives. Ethylfurylcarbinol was prepared in 1884 by the action of diethylzinc on furfural.[274] Some years later, Grignard[275] synthesized the related isopentylfurylcarbinol from furfural by the reaction which bears his name. The early attempts to effect the Grignard reaction with phenylmagnesium bromide, and with benzylmagnesium chloride, gave only the coupling products, biphenyl and *sym*-diphenylethane, respectively[276] (see also [277]). However, Peters and Fischer[278] (see also [279]) later demonstrated that the Grignard reagent reacts normally[m] with furfural, although formation of the carbinol is generally accompanied by considerable resin formation. They successfully prepared phenylfurylcarbinol and a number of related types by this procedure using ether as the medium. According to Kuznetsov,[282] when the reaction is carried out in boiling xylene, with an excess of the Grignard reagent, the furan ring is cleaved with the formation of compounds of the general type RCH=CHCH =C(OMgX)R which on saponification give rise to the corresponding α-ketols, $RCH=CHCH_2COCH(OH)R$.[282]

[m] More recently an anomalous Grignard reaction has been reported by Kursanov and Solodkov[144] (see also [280]). Cyclohexylmagnesium iodide is apparently oxidized by furfural (and by benzaldehyde) since the products of the reaction are difurfurylidenecyclohexanone (p. 474) and furfuryl alcohol. However, Chichibabin[281] reports cyclohexylfurylcarbinol from furfural and cyclohexylmagnesium bromide in ether.

[268] Šorm and Brandejs, *Collection Czechoslov. Chem. Communs.*, **12**, 444 (1947); *C. A.*, **43**, 2988 (1949).

[269] Šorm and Arnold, *Collection Czechoslov. Chem. Communs.*, **12**, 467 (1947); *C. A.*, **43**, 214 (1949).

[270] Freund and Immerwahr, *Ber.*, **23**, 2845 (1890).

[271] Hofmann, *J. Am. Chem. Soc.*, **67**, 421 (1945).

[272] Hofman (to Ciba Pharmaceutical Products, Inc.), U. S. Pat. 2,432,016 (1947); *C. A.*, **42**, 1969 (1948).

[273] Hofmann, Brit. Pat. 615,908 (1949); *C. A.*, **43**, 5805 (1949).

[274] Pawlinoff and Wagner, *Ber.*, **17**, 1967 (1884).

[275] Grignard, *Ann. chim. phys.*, (7) **24**, 468 (1901).

[276] Hale, McNally and Pater, *Am. Chem. J.*, **35**, 68 (1906).

[277] Mahood and Jordan, *Science*, **60**, 453 (1924).

[278] Peters and Fischer, *J. Am. Chem. Soc.*, **52**, 2079 (1930).

[279] Yur'ev and Gragerov, *Zhur. Obshchei Khim. J. Gen. Chem.*, **19**, 724 (1949); *C. A.*, **44**, 1092 (1950).

[280] Katsnel'son and Dubinin, *Compt. rend. acad. sci. U.R.S.S., N. S.*, **4**, 405 (1936); *C. A.*, **31**, 3449 (1937).

[281] Chichibabin, *Congr. chim. ind. Compt. rend.*, **11**, 563 (1932); *C. A.*, **26**, 3778 (1932).

[282] Kuznetsov, *J. Gen. Chem. U.S.S.R.*, **9**, 2263 (1939); *C. A.*, **34**, 5052 (1940).

Except where otherwise noted, the secondary alcohols (III) listed below were obtained from furfural by reaction with the appropriate organomagnesium halide.[n] When pure, they are colorless liquids, slightly soluble in water, and completely miscible with alcohol, ether, chloroform and benzene. Like furfuryl alcohol, they are sensitive toward acidic reagents, and are subject to autoxidation on standing in air.

$$C_4H_3O—CHO + RMgX \rightarrow C_4H_3O—CH(OMgX)R \rightarrow C_4H_3O—CH(OH)R$$
III

2-Furylcarbinols:

Methylfurylcarbinol: [1-(2-(furyl)ethyl alcohol]; III (R = CH_3); b.p. 70° (15 mm). 76–77° (23 mm.), 162–163°; d_4^{20} 1.0790, d_{25}^{25} 1.0771, n_D^{15} 1.4827, n_D^{20} 1.4808, n_D^{25} 1.4785.[278, 279, 281, 283] For resolution into its optical antipodes, see Duveen and Kenyon.[283, 284] **Acetate,** b.p. 85° (18 mm.), 177° (760 mm.); n_D^{15} 1.4618. ***p*-Xenylurethan,** m.p. 114°. **Hydrogen phthalate,** m.p. 80°. **Ethers:** methyl, b.p. 137–139°; n_D^{16} 1.4532; d_4^{14} 0.9912; ethyl, b.p. 150–152°; n_D^{18} 1.4502; d_4^{18} 0.9658. On heating with alcoholic hydrogen chloride, the ethers are cleaved to δ-alkyllevulinic esters.[285, 286] (see also Chapter 14). The **chloride** (no constants) was prepared by the action of thionyl chloride on the carbinol in pyridine. Reaction of the chloride with aqueous potassium cyanide, and subsequent hydrolysis gave rise to 5-ethyl-2-furoic acid [287] (see also p. 550). The **bromide** (no constants), derived from the carbinol and phosphorus tribromide in pyridine, behaved similarly to the chloride when treated with aqueous potassium cyanide.[287] Several amino compounds related to the carbinol have been reported:

$C_4H_3O—CH(CH_3)NRR'$

R	R'	Physical constants (°C.)	Ref.
H	n-C_5H_{11}	b.p. 102–103 (15 mm.) d_4^{20} 0.913 n_D^{20} 1.4681	288
H	2-pyridyl	b.p. 110–112 (1.6 mm.) **picrate,** m.p. 158.5–159.5	228
H	2-thiazolyl	m.p. 84.5–86.5 b.p. 125–127 (0.5 mm.) **picrate,** m.p. 180–181	228
$(CH_3)_2NCH_2CH_2$	2-pyridyl	b.p. 121–126 (1.0 mm.) **fumarate,** m.p. 136	228

[n] Related 2-furylcarbinols possessing olefinic and acetylenic side chains are included with the furylalkenols (p. 262).

[283] Duveen and Kenyon, *J. Chem. Soc.*, **1936,** 621.

[284] Duveen and Kenyon, *Bull. soc. chim.*, **7,** 165 (1940).

[285] Ushakov and Kucherov, *J. Gen. Chem. U.S.S.R.*, **14,** 1080 (1944); *C. A.*, **40,** 7185 (1946).

[286] Kucherov, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20,** 1885 (1950); *C. A.*, **45,** 2928 (1951).

[287] Reichstein and Zschokke, *Helv. Chim. Acta*, **15,** 1124 (1932).

[288] Emling, Beatty and Stevens, *J. Am. Chem. Soc.*, **71,** 703 (1949).

Ethylfurylcarbinol: [1-(2-furyl)propyl alcohol]; III (R = C_2H_5); b.p. 57–58° (6 mm.), 89–90° (23 mm.), 181–183° (—); d_4^{20} 1.0432, d_{20}^{20} 1.0474; n_D^{20} 1.4759; **acetate,** b.p. 98° (37 mm.). **Ethyl ether,** b.p. 164–166° (—); d_4^{18} 0.9547; n_D^{18} 1.4485[278, 279, 281, 282, 285, 289] (see also [274, 290]). For catalytic hydrogenation, see Pierce and Adams.[291] **Amine,** b.p. 83–85° (14 mm.); picrate, m.p. 168°. Obtained by reduction of the oxime of furyl ethyl ketone,[288] and also by reduction of the intermediate product derived from 2-furonitrile and ethylmagnesium iodide.[292] The secondary amine, **N-butyl-N-1-(2-furyl)propylamine,** b.p. 108–109° (25 mm.); d_4^{20} 0.907; n_D^{20} 1.4635, was obtained by the action of ethylmagnesium bromide on the appropriate furfuraldimine.[288]

***n*-Propylfurylcarbinol:** [1-(2-furyl)butyl alcohol]; III (R = *n*—C_3H_7); b.p. 76–77° (5 mm.), 85–86° (10 mm.), 195–198° (atm.); d_4^{20} 1.0197, d_{25}^{25} 1.0179; n_D^{20} 1.4789, n_D^{25} 1.4768.[278, 279, 282] **Phenylurethan,** m.p. 79.5°.[293] **Acetate,** b.p. 96–97° (22 mm.).[294] For reaction with 3-sulfolene, see Morris and Van Winkle.[295] For catalytic hydrogenation, see [293]. **Chloride,** b.p. 90–91° (6 mm.).[294] **N-propyl-N-1-(2-furyl)butylamine,** b.p. 107–108° (24 mm.); d_4^{20} 0.904; n_D^{20} 1.4634.[288]

***i*-Propylfurylcarbinol:** [1-(2-furyl)isobutyl alcohol]; III (R = *i*—C_3H_7); b.p. 99–100° (38 mm.); d_{25}^{25} 1.0111; n_D^{25} 1.4715; **acetate,** b.p. 99–100° (35 mm.).[278] **Ethyl ether,** b.p. 168–170° (—); d_4^{19} 0.9393; n_D^{17} 1.4556, was oxidized by potassium permanganate to give a small amount of α-ethoxyisovaleric acid.[285]

***n*-Butylfurylcarbinol:** [1-(2-furyl)pentyl alcohol]; III (R = *n*—C_4H_9); b.p. 94–96° (2 mm.); 100–102° (2 mm.); d_4^{20} 0.9914; d_{25}^{25} 0.9931; n_D^{25} 1.4710[278, 291] (see also [295a]). **Ethyl ether,** b.p. 79–81° (7 mm.), was oxidized to α-ethoxyhexanoic acid by the action of potassium permanganate.[286] For reduction with sodium and alcohol in liquid ammonia, see Birch.[45] The secondary amine, **N-ethyl-N-1-(2-furyl)pentylamine,** b.p. 105.5–106.5° (23 mm.); d_4^{20} 0.909; n_D^{20} 1.4636.[288]

***i*-Butylfurylcarbinol:** [1-(2-furyl)isopentyl alcohol]; III (R = *i*—C_4H_9); b.p. 81–82° (5 mm.), 92–94° (5 mm.), 102–103° (10 mm.); d_4^{20} 1.0320, d_{25}^{25} 0.9904; n_D^{25} 1.4687; **acetate,** b.p. 119–120° (30 mm.).[278, 282, 286] **Ethyl ether,** b.p. 75–77° (7 mm.), was converted into *i*-C_4H_9—CH(OEt)COOH with potassium permanganate.[286]

***t*-Butylfurylcarbinol:** [1-(2-furyl)-2,2-dimethylpropyl alcohol]; III (R = *t*—C_4H_9); b.p. 75–78° (8 mm.); n_D^{18} 1.4820; d_4^{17} 1.0227.[285]

***n*-Pentylfurylcarbinol:** [1-(2-furyl)hexyl alcohol]; III (R = *n*—C_5H_{11}); b.p. 106–108° (6 mm.).[282] Secondary amine, **N-methyl-N-1-(2-furyl)hexylamine,** b.p. 75–76° (3 mm.); d_4^{20} 0.913; n_D^{20} 1.4649.[288]

***i*-Pentylfurylcarbinol:** [1-(2-furyl)isohexyl alcohol]; III (R = *i*—C_5H_{11}); b.p. 110° (8 mm.), 202–204° (—); d_4^{12} 0.9882; n_D^{12} 1.4794; **acetate,** b.p. 123–124° (14 mm.).[275, 289] Secondary amine, **N-methyl-N-[1-(2-furyl)-4-methyl]pentylamine,** b.p. 67.5–68.5° (4 mm.); d_4^{20} 0.913; n_D^{20} 1.4644.[288]

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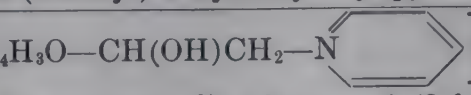
[289] Chelintzev, *Bull. soc. chim.*, [5] **4,** 819 (1937).
[290] Douris, *Compt. rend.*, **157,** 722 (1913).
[291] Pierce and Adams, *J. Am. Chem. Soc.*, **47,** 1098 (1925).
[292] Erlenmeyer and Simon, *Helv. Chim. Acta*, **24,** 1210 (1941).
[293] Kondo and Takeda, *J. Pharm. Soc. Japan*, **55,** 734 (1935); *C. A.*, **29,** 7324 (1935).
[294] Jolkver, *Rec. trav. chim.*, **28,** 439 (1909).
[295] Morris and Van Winkle (to Shell Development Co.), U. S. Pat. 2,504,098 (1950); *C. A.*, **44,** 6887 (1950).
[295a] Nazarov and Fisher, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20,** 1114 (1950); *C. A.*, **44,** 9460 (1950).

Cyclopentylfurylcarbinol: III (R = C_5H_9); b.p. 114–116° (8 mm.).[296]

Cyclohexylfurylcarbinol: III (R = C_6H_{11}); b.p. 132–134° (13 mm.); d_4^{15} 1.0581.[281]

Benzylfurylcarbinol: [1-(2-furyl)-2-phenylethyl alcohol]; III (R = $C_6H_5CH_2$); b.p. 116.5–118° (—); d_4^{20} 1.1184; n_D^{20} 1.5489.[297] In earlier work, it was found that the pure carbinol could not be isolated by distillation, because of facile dehydration to 2-(2-phenylvinyl)furan even in high vacuum.[163]

1-[2-(2-Furyl)-2-hydroxyethyl]pyridinium perchlorate:



$^+ClO_4^-$; no constants. Oxidized by permanganate to the corresponding ketone, 1-(2-furacyl)pyridinium perchlorate, m.p. 146°, which was converted into 2-furoylformic acid.[298]

Tritylfurylcarbinol: [1-(2-furyl)-2,2,2-triphenylethyl alcohol]; III [R = $(C_6H_5)_3C$]; m.p. 125°; obtained by reaction of furfural with triphenylmethylsodium.[299]

Phenethylfurylcarbinol: [1-(2-furyl)-3-phenylpropyl alcohol]; III (R = $C_6H_5CH_2CH_2$); b.p. 165–167° (10 mm.); d_{15}^{13} 1.102; n_D^{13} 1.559. Loses the elements of water on distillation to give furylphenylpropene.[300] With alcoholic hydrochloric acid it is cleaved to 7-phenyl-4-oxoheptanoic ester.[286]

(β-2-Furylethyl)furylcarbinol: [1,3-di(2-furyl)propyl alcohol]; III (R = C_4H_3O—CH_2CH_2); b.p. 99–100° (0.25 mm.); n_D^{25} 1.5133; d_4^{25} 1.1388; **3,5-dinitrobenzoate,** m.p. 93.5–94.5° Derived from furfurylideneacetylfuran (p. 434) by catalytic hydrogenation.[301, 302]

(β-Phenylethyl)furylcarbinol: [1-furyl-3-phenylpropyl alcohol]; III (R = C_6H_5-CH_2CH_2); b.p. 109–111° (0.22 mm.); d_4^{25} 1.0934; n_D^{25} 1.5441; by catalytic reduction of benzylideneacetylfuran.[303]

(ω-2-Furylbutyl)furylcarbinol: [1,5-difurylpentyl alcohol]; III [R = C_4H_3O—$(CH_2)_4$]; b.p. 134–140° (0.8 mm.); d_4^{25} 1.0929; n_D^{25} 1.5088; by catalytic reduction of the condensation product of 3-(2-furyl)acrolein and 2-furyl methyl ketone.[303]

Phenylfurylcarbinol: III (R = C_6H_5); b.p. 122–125° (2 mm.); 145° (13 mm.); d_{25}^{25} 1.1423; n_D^{25} 1.5522.[278, 281] Paul[304] modified earlier procedures, and was able to obtain the product in 65 per cent yield from furfural and an excess of phenylmagnesium bromide in ether. It loses water at 170°, and is reduced by sodium in alcohol to furylphenylmethane.[304] The **β-dimethylaminoethyl ether,** (b.p. 100–102° (0.035 mm.)), the furyl isostere of Benadryl, was tested for its antihistaminic activity by Biel.[237]

The corresponding **amine,** C_4H_3O—$CH(NH_2)C_6H_5$, b.p. 144–145° (17 mm.); acetyl derivative, m.p. 127°, was obtained by reduction of the oxime of phenyl furyl ketone with sodium in alcohol.[178, 305] The amine hydrochloride was treated with po-

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[296] Katsnel'son and Kondakova, *Compt. rend. acad. sci. U.R.S.S.*, **17,** 367 (1937); *C. A.*, **32,** 7022 (1938).

[297] Marko and P'yankov, *Khim. Referat. Zhur.*, **4,** 49 (1941); *C. A.*, **37,** 5058 (1943).

[298] Kröhnke, *Chem. Ber.*, **80,** 298 (1947).

[299] Schlenk and Ochs, *Ber.*, **49,** 608 (1916).

[300] Paul, *Compt. rend.*, **202,** 854 (1936).

[301] Alexander and Smith, *J. Am. Chem. Soc.*, **71,** 735 (1949).

[302] Alexander (to the United States of America, as represented by the Secy. of Agriculture), U. S. Pat. 2,532,279 (1950); *C. A.*, **45,** 3423 (1951).

[303] Alexander, Hafner, Smith and Schniepp, *J. Am. Chem. Soc.*, **72,** 5506 (1950).

[304] Paul, *Compt. rend.*, **202,** 1444 (1936).

tassium cyanate to obtain N-(α-furfurylbenzyl)urea, $C_4H_3O—CH(NHCONH_2)C_6H_5$, m.p. 80°, which decomposed on standing with loss of ammonia.[178]

o- or p-Hydroxyphenylfurylcarbinol: III (R = HOC_6H_4); presumably a mixture of the two isomers represents the first-formed products of the reaction of furfural with phenol. Further reaction, of course, produces the well-known furfural-phenol plastics.[306]

o- or p-Methoxyphenylfurylcarbinol: III (R = $CH_3OC_6H_4$); no constants; obtained as intermediate products from furfural and *o*- and *p*-methoxyphenylmagnesium bromides. Reduction replaced the hydroxyl by hydrogen, giving rise to the corresponding methoxyphenylfurylmethanes. Catalytic hydrogenation saturates the furan ring leaving the hydroxyl groups intact.[146]

1-Naphthylfurylcarbinol: III (R = $C_{10}H_7$); b.p. 178–179° (4 mm.); **methyl ether,** b.p. 152–154° (3 mm.); n_D^{24} 1.425[290] (see also [297]).

Miscellaneous. Among the compounds listed here are several amines, the parent secondary alcohols of which have not been described.

1-Phenyl-2-(2-furyl)ethylamine: $C_4H_3O—CH_2CH(NH_2)C_6H_5$; b.p. 158–160° (30 mm.); hydrochloride, m.p. 206–208° (dec.). Obtained by reduction of 2-(2-phenyl-2-nitrovinyl)furan, $C_4H_3O—CH{=}C(C_6H_5)NO_2$.[307]

2-(2-Furyl)isopropylamine: $C_4H_3O—CH_2CH(NH_2)CH_3$; b.p. 66–68° (21 mm.); picrate, m.p. 160°. From the oxime of furylacetone, by reduction with sodium in alcohol[292] (see also [308]).

4-(2-Furyl)-2-butanol: $C_4H_3O—CH_2CH_2CHOHCH_3$; b.p. 127–128° (55 mm.); d_4^{25} 1.0192; n_D^{25} 1.4744; **3,5-dinitrobenzoate,** m.p. 63–64°; by catalytic reduction of furfurylideneacetone.[303] Also obtained, in admixture with furfurylacetone, by reduction of furfurylideneacetone by the action of fermenting yeast.[309] The corresponding **amine,** b.p. 102° (25 mm.), 190° (760 mm.); n_D^{28} 1.4730; was derived from furfurylideneacetone by aminative reduction; the secondary amine, $(C_4H_3O—CH_2CH_2CHCH_3)_2NH$, b.p. 128° (0.05 mm.); n_D^{29} 1.4942; was obtained as a by-product of this synthesis[310] (see also [292, 311]).

1-Phenyl-3-(2-furyl)propyl alcohol: $C_4H_3O—CH_2CH_2CH(OH)C_6H_5$; b.p. 166–167° (8 mm.); d_4^{20} 1.10; n_D 1.553; **phenylurethan,** m.p. 95.5–96°; **acetate,** b.p. 171–172° (11 mm.); d_4^{20} 1.09; n_D 1.526. The alcohol was prepared by reduction of furfurylideneacetophenone using sodium amalgam.[312, 313] **Ethyl ether,** b.p. 145–147° (11 mm.); d_4^{20} 1.055; n_D 1.545. **Chloride,** b.p. 154° (—); d_4^{15} 1.13; n_D 1.552; from the alcohol by the action of phosphorus pentachloride. On heating over sodium acetate in glacial acetic acid, dehydrohalogenation takes place with formation of 2-(3-phenyl-2-propenyl)furan.[312]

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[305] Marquis, *Ann. chim. phys.*, (8), **4**, 196 (1905).

[306] Porai-Koshitz, Kudryavtzev and Mashkileizon, *J. Applied Chem. U.S.S.R.*, **6**, 685 (1933); *C. A.*, **28**, 4055 (1934).

[307] Reichert and Kuhn, *Ber.*, **74**, 328 (1941).

[308] Hass, Susie and Heider, *J. Org. Chem.*, **15**, 8 (1950).

[309] Fischer, Wiedemann and Robertson, *Ann.*, **520**, 52 (1935).

[310] Haskelberg, *J. Am. Chem. Soc.*, **70**, 2811 (1948).

[311] Fujita, *J. Pharm. Soc. Japan*, **519**, 456 (1925); *C. A.*, **20**, 412 (1926).

[312] Semmler and Ascher, *Ber.*, **42**, 2355 (1909).

[313] Semmler, *Ber.*, **39**, 726 (1906).

1,3-Difurfurylisopropyl alcohol: (1,5-difuryl-3-pentanol); $(C_4H_3O—CH_2CH_2)_2CHOH$; b.p. 112–114° (0.14 mm.); d_4^{25} 1.1006; n_D^{25} 1.5092; **3,5-dinitrobenzoate,** m.p. 87–88°; **hydrogen phthalate,** m.p. 93–94°; by catalytic reduction of difurfurylideneacetone.[303] The corresponding **amine,** b.p. 254–255° (2 mm.) was prepared from the same source by aminative reduction.[314]

1,3-Difurfuryl-1-methylisopropyl alcohol: (1,5-difuryl-2-methyl-3-pentanol); $C_4H_3O—CH_2CH(CH_3)CHOHCH_2CH_2—C_4H_3O$; b.p. 110–112° (0.14 mm.); d_4^{25} 1.0833; n_D^{25} 1.5074; by catalytic reduction of furfurylidenemethyl furfurylideneëthyl ketone.[303]

1,9-Difuryl-5-nonyl alcohol: $C_4H_3O—(CH_2)_4CHOH(CH_2)_4—C_4H_3O$; b.p. 148–152° (0.15 mm.); d_4^{25} 1.044; n_D^{25} 1.5046; **hydrogen phthalate,** m.p. 70–73°; by catalytic reduction of bisfurylacroleinacetone.[303]

Tertiary Alcohols and Their Derivatives. *2-Furylcarbinols.* Tertiary alcohols of type IV (where R = R′) are obtainable by the action of the appropriate Grignard reagent on 2-furoic ester (see p. 518). Similar treatment of 2-acylfurans likewise gives rise to IV, where R and R′ may be the same or different depending upon the selection of reactants. The alcohols listed below were all prepared by one or both of these procedures.

$$C_4H_3O—CO—R \xrightarrow{R'MgX} \xrightarrow{HOH} \underset{IV}{C_4H_3O—C(OH)RR'}$$

Dimethylfurylcarbinol: IV (R = R′ = CH_3); b.p. 71–72° (15 mm.), 161–163° (atm.); m.p. 10–11°; n_D^{25} 1.4700; d_{25}^{25} 1.037.[315] For attempted conversion to the corresponding chloride and bromide, see Reichstein and Zschokke.[287] Dehydration over sodium acetate in acetic anhydride gives rise to 2-isopropenylfuran.[315, 316]

Methylethylfurylcarbinol: IV (R = CH_3; R′ = C_2H_5); b.p. 77–78° (19 mm.); d_{25}^{25} 1.023; n_D^{25} 1.4729. Was dehydrated as above to give a mixture of the two possible butenylfurans which was hydrogenated to 2-*sec*-butylfuran.[47]

Diethylfurylcarbinol: IV (R = R′ = C_2H_5); b.p. 92–95° (14 mm.), 82° (16 mm.). Obtained by the action of ethylmagnesium bromide on 2-furoic ester,[317] and on furoyldimethylacetic ester[318] (see also [276]). For discussion of the latter reaction, see p. 605).

Dipropylfurylcarbinol: IV (R = R′ = C_3H_7); b.p. 146–148° (20 mm.).[319]

Di-*n*-butylfurylcarbinol: IV (R = R′ = *n*—C_4H_9); b.p. 128–131° (14 mm.); d_{25}^{25} 0.9251; n_D^{25} 1.4703.[317]

Di-*i*-butylfurylcarbinol: IV (R = R′ = *i*—C_4H_9); b.p. 157–159° (18 mm.).[319]

Di-*t*-butylfurylcarbinol: IV (R = R′ = *t*—C_4H_9); b.p. 80–85° (1 mm.); d_4^{34} 0.9486 n_D^{34} 1.4749. Analysis shows product to be impure.[164]

Di-*i*-pentylfurylcarbinol: IV (R = R′ = *i*—C_5H_{11}); b.p. 166–168° (20 mm.).[319]

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[314] Zerweck, "Furfural as a Starting Material for New Solvents and Plasticizers," PB No. **42436,** U. S. Dept. Commerce, 1940.

[315] Bachman and Heisey, *J. Am. Chem. Soc.*, **71,** 1985 (1949).

[316] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15,** 1118 (1932).

[317] Dounce, Wardlow and Connor, *J. Am. Chem. Soc.*, **57,** 2556 (1935).

[318] Mironescu and Ioanid, *Bul. soc. chim. Romania*, **17,** 107 (1935); *C. A.*, **30,** 1053 (1936).

[319] Kuznetsov, *J. Gen. Chem. U.S.S.R.*, **12,** 631 (1942); *C. A.*, **38,** 1494 (1944).

Dibenzylfurylcarbinol: IV (R = R′ = $C_6H_5CH_2$); m.p. 82.7°; **methyl ether,** m.p. 61.2°.[276]

Alkylarylfurylcarbinols: C_4H_3O—C(OH)RR′. The carbinols listed below were prepared by treating furyl phenyl ketone and a number of its *p*-substituted derivatives with the appropriate alkylmagnesium halide.[320]

R	R′	b.p. (°C.)
C_2H_5	C_6H_5	128 (13 mm.)
C_2H_5	*p*-$CH_3C_6H_4$	136 (12 mm.)
C_2H_5	*p*-ClC_6H_4	146 (12 mm.)
C_3H_7	C_6H_5	134 (12 mm.)
C_3H_7	*p*-$CH_3C_6H_4$	140 (12 mm.)
C_3H_7	*p*-ClC_6H_4	150 (11 mm.)
C_3H_7	*p*-BrC_6H_4	173 (12 mm.)
i-C_4H_9	C_6H_5	138 (12 mm.)
i-C_4H_9	*p*-$CH_3C_6H_4$	145 (13 mm.)
i-C_4H_9	*p*-ClC_6H_4	156 (11 mm.)
i-C_4H_9	*p*-BrC_6H_4	176 (13 mm.)

Benzylphenylfurylcarbinol: IV (R = $C_6H_5CH_2$; R′ = C_6H_5); b.p. 202–203° (—). When treated with a large excess of formic acid on a water bath, the carbinol lost the elements of water with formation of α-2-furylstilbene.[321]

Diphenylfuryl carbinol: IV (R = R′ = C_6H_5); m.p. 91°, 92.4°[276, 322] (see also [318]). Reduction, using zinc dust in acetic acid gave rise to diphenylfurylmethane.[322] Boiling with dilute acetic acid produced bisdiphenylfurylmethyl ether.[323] Conversion to the **chloride** by the action of thionyl chloride was successful, although it was not isolated due to its great instability, but was used directly in ether solution. Thus, the chloride on treatment with mercury produced *sym*-tetraphenyl-di-2-furylethane. With the appropriate alcohol in the presence of pyridine, the chloride was converted into the corresponding **ethers:** methyl, m.p. 108–108.5°; ethyl, m.p. 107–108°; *n*-propyl, m.p. 106–107°; *i*-propyl, m.p. 85–86°; benzyl, m.p. 89–90°C.[324] For cleavage of the methyl ether to δ,δ-diphenyllevulinic acid, see Ushakov and Kucherov.[325]

The **tertiary amine,** C_4H_3O—$C(C_6H_5)_2$—$N(C_2H_5)_2$, m.p. 181°[326]

Related diarylfurylcarbinols: C_4H_3O—C(OH)RR′, were prepared by Maxim and Popesco.[320]

Di-*p*-xenylfurylcarbinol: IV (R = R′ = *p*—$C_6H_5C_6H_4$); m.p. 149–150°; from ethyl furoate and *p*-xenylmagnesium bromide. Converted to the corresponding **chloride** (not isolated), and thence to the **methyl ether,** m.p. 94–95°. The chloride, with mercury, gave rise to *sym*-tetra-*p*-xenyl-di-2-furylethane.[324]

***ms*-Furylquinols of anthracene: 9-Furyl-10-phenyl-9,10-dihydroxy-9,10-dihydroanthracene,** II (R = C_6H_5), m.p. 204°. The method of synthesis involved the interaction of 2-furylmagnesium bromide with 10-phenyl-10-hydroxy-9-anthrone, I

[320] Maxim and Popesco, *Bul. soc. chim. Romania*, **16,** 89 (1934); *C. A.*, **29,** 4355 (1935).

[321] Buu-Hoi and Hiong-Ki-Wei, *Compt. rend.*, **220,** 175 (1945).

[322] Mahood and Aldrich, *J. Am. Chem. Soc.*, **52,** 4477 (1930).

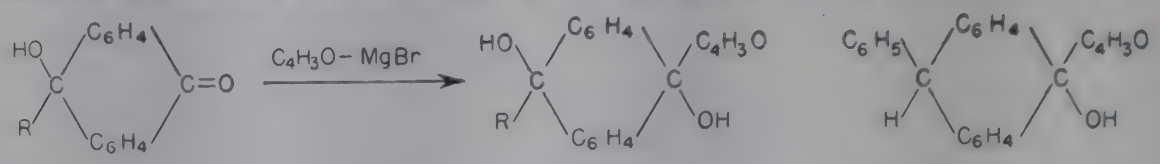
[323] Gilman, Franz, Hewlett and Wright, *J. Am. Chem. Soc.*, **72,** 3 (1950).

[324] French and Smith, *J. Am. Chem. Soc.*, **67,** 1949 (1945).

[325] Ushakov and Kucherov, *J. Gen. Chem. U.S.S.R.*, **14,** 1073 (1944); *C. A.*, **40,** 7185 (1946).

[326] Maxim, Zugravescu and Fulga, *Bull. soc. chim.*, **6,** 1339 (1939).

(R = C_6H_5). The related **9,10-difuryl compound,** II (R = C_4H_3O), m.p. 213°, was similarly derived from anthraquinone. A number of the corresponding ethers were prepared by the action of the appropriate alkyl iodide and powdered potassium hydroxide. Attempted etherification using an alcohol and hydrochloric acid gives rise to products related to levulinic ester (see pp. 172), from which it is ap-



I II III

parent that II is reacting as a 2-furylcarbinol. The related monoquinol, **9-furyl-10-phenyl-9-hydroxy-9,10-dihydroanthracene,** III, m.p. 169°, behaves differently under these conditions, giving rise to 2-(10-phenyl-9-anthryl)furan by straightforward dehydration.[327]

Miscellaneous:

2-Methyl-4-(2-furyl)-2-butanol: $C_4H_3O—CH_2CH_2C(CH_3)_2OH$; b.p. 93.5–94° (8 mm.); d_4^{25} 0.9972; n_D^{25} 1.4745; **phenylurethan,** m.p. 126.5–127°; **acetate,** b.p. 83–85° (3 mm.); d_4^{25} 1.0188; n_D^{25} 1.4583. By the action of methylmagnesium iodide on furfurylacetone.[328]

1-(2-Furyl)-3-methyl-3-pentanol: $C_4H_3O—CH_2CH_2C(CH_3)(OH)C_2H_5$; b.p. 83.5–84.5° (2 mm.); d_4^{25} 0.9926; n_D^{25} 1.4780; **phenylurethan,** m.p. 84.5–85°. From furfurylacetone and ethylmagnesium bromide.[328]

2,3-Dimethyl-4-(2-furyl)-2-butanol(?): $C_4H_3O—CH_2CH(CH_3)C(CH_3)_2OH$; b.p. 82.5° (3.5 mm.); d_4^{25} 0.9923; n_D^{25} 1.4779; **phenylurethan,** m.p. 91–91.5°.[328] The structure of this compound, which is an isomer of the preceding alcohol, is in some doubt. It was obtained from methyl ethyl ketone and furfural, the intermediate furfurylidene compound being reduced and then treated with MeMgI.[328] However, there is doubt regarding the structure of the intermediate furfurylidene derivative (see p. 454). It is unfortunate that Kasiwagi[328] did not make a mixed m.p. determination of the phenylurethans of this and the preceding alcohol. The two alcohols may be identical, and the structure of the preceding alcohol is not in doubt.

1-(2-Furyl)-2,3-dimethyl-3-pentanol: $C_4H_3O—CH_2CH(CH_3)C(CH_3)(OH)C_2H_5$; b.p. 93° (3.5 mm.); d_4^{25} 0.9895; n_D^{25} 1.4800; from MeMgI and 1-furyl-2-methyl-3-pentanone, the latter being obtained by reduction of the furfurylidene derivative of diethyl ketone.[328]

2,4-Di-*i*-pentyl-4-(2-furyl)-2-butanol: $C_4H_3O—CH(i—C_5H_{11})CH_2C(i—C_5H_{11})(CH_3)OH$; b.p. 170–180°; d_{13} 0.9243; n^{13} 1.4703; by the action of two moles of *i*-pentylmagnesium iodide on furfurylideneacetone.[329]

Nuclear Homologs

Primary Alcohols and Their Derivatives.

5-Methylfurfuryl alcohol: [5-methyl-2-furylcarbinol]; $CH_3—C{=}CHCH{=}C—CH_2OH$; (O)

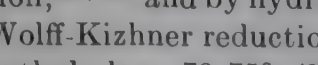
[327] Étienne and Brisson, *Compt. rend.*, **224,** 1775 (1947); *ibid.*, **227,** 208, 288 (1948); Brisson, *ibid.*, **227,** 1103 (1948).

[328] Kasiwagi, *Bull. Chem. Soc. Japan*, **2,** 310 (1927); *C. A.*, **22,** 778 (1928).

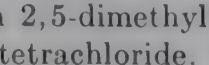
[329] Chelintzev and Till, *Uchenye Zapiski Saratov Gosudarst. Univ. N. G. Chernyshevskogo, Khim.*, **15,** 24 (1940); *C. A.*, **35,** 6953 (1941).

b.p. 81–83° (11 mm.), 194–196° (744 mm.); d_4^{20} 1.0769; n_D^{20} 1.4853; ***p*-nitrobenzoate,** m.p. 84–85°; **diphenylurethan,** m.p. 52–53°. The alcohol was obtained from 5-methylfurfural by the Cannizzaro reaction,[330, 331] and by hydrogenation over Adams catalyst.[331] It has also been prepared by Wolff-Kizhner reduction of the hydrazone of 5-hydroxymethylfurfural.[332] **Ethers:** methyl, b.p. 70–75° (32 mm.); n_D^{19} 1.4608; ethyl, b.p. 65–68° (12 mm.); n_D^{17} 1.4578.[70] For resinification studies, see Dinelli and Marini-Bettolo.[70] The **bromide** was prepared from 2,5-dimethylfuran by the action of N-bromosuccinimide in anhydrous carbon tetrachloride. It is a yellowish oil, b.p. 70° (2.5 mm.) which distills with *violent decomposition*.[142] The **chloride,** b.p. 30–35° (0–2 mm.), was obtained by placing the alcohol in reaction with thionyl chloride in pyridine. It is reported to be even more unstable than furfuryl chloride.[331, 332] The known amino and sulfur derivatives are listed elsewhere (pp. 240, 249).

3-Methylfurfuryl alcohol:

[(3-methyl-2-furyl)carbinol];  b.p. 79–81° (3 mm.);

d_4^{20} 1.0917; n_D^{20} 1.4871–1.4880; **α-naphthylurethan,** m.p. 151–153° (dec). Prepared from 3-methyl-2-furoic acid by reduction with lithium aluminum hydride and from 3-furylmethylmagnesium chloride by the action of formaldehyde[333] (see also p. 265).

2-(5-Phenyl-2-furyl)ethyl alcohol:  The alcohol is unreported, but the corresponding amine (HCl salt, m.p. 205–206°) has been obtained in low yield from 3-(5-phenyl-2-furyl)propionic acid by the Curtius reaction.[334]

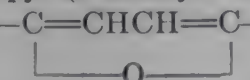
2-(5-*p*-Methoxyphenyl-2-furyl)ethyl alcohol: The corresponding amine (HCl salt, m.p. 240°) was prepared as in the preceding preparation from 3-(5-*p*-methoxyphenyl-2-furyl)propionic acid.[334]

5-Furfurylfurfuryl alcohol: [5-hydroxymethyl-2,2′-difurylmethane];

 b.p. 131–133° (2.5 mm.); d_{25}^{25} 1.178–1.179; n_D^{20} 1.5270; **α-naphthylurethan,** m.p. 107–108°; **benzoate,** m.p. 70–71°. The alcohol was isolated as an intermediate product in the resinification of furfuryl alcohol.[32]

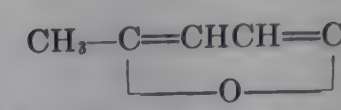
5-(5-Furfurylfurfuryl)furfuryl alcohol(?):  b.p. 199–202° (3 mm.) with some decomposition; d_{25}^{25} 1.192; n_D^{20} 1.5428, n_D^{25} 1.5411; isolated from partially resinified furfuryl alcohol.[32]

Secondary Alcohols and Their Derivatives.

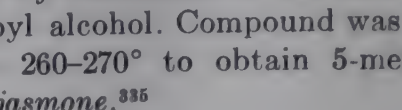
***i*-Propyl-(5-methyl-2-furyl)carbinol:** [1-(5-methyl-2-furyl)isobutyl alcohol];  b.p. 97–98.5° (17 mm.); d_4^{18} 0.9973; n_D^{18} 1.4776. **Ethyl ether,** b.p. 73–75° (10 mm.); d_4^{19} 0.9393; n_D^{17} 1.4556.[285]

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[330] Blanksma, *Chem. Weekblad*, **9**, 186 (1912); *C. A.*, **6**, 1433 (1912).
[331] Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).
[332] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 249 (1932).
[333] Sherman and Amstutz, *J. Am. Chem. Soc.*, **72**, 2195 (1950).
[334] Robinson and Todd, *J. Chem. Soc.*, **1939**, 1743.

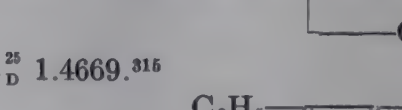
1-(5-Methyl-2-furyl)hexan-3-ol:  ; b.p. 102–109° (3 mm.). Obtained by reduction of the corresponding ketone with aluminum isopropoxide in isopropyl alcohol. Compound was dehydrated over phosphoric acid-activated carbon at 260–270° to obtain 5-methyl-2-hexenylfuran in connection with the synthesis of *jasmone*.[335]

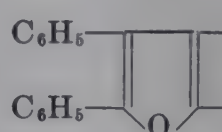
Tertiary Alcohols and Their Derivatives.

4-(5-Methyl-2-furyl)-2-R-2-butanol: 

The series listed below was prepared by the action of the appropriate Grignard reagent on 4-(5-methyl-2-furyl)-2-butanone.[336]

R	Physical constants b.p. (°C.)	n_D^{25}
n-C_4H_9	101–106 (1 mm.)	1.4740
$C_6H_5CH_2$	154–157 (2 mm.)	1.5347
cyclohexyl	131–161 (1 mm.)	1.5010
C_6H_5	151–154 (9 mm.)	1.5386
p-$CH_3C_6H_4$	144.5–146 (1 mm.)	1.5355
1-$C_{10}H_7$	219–219.5 (9 mm.)	1.601

Dimethyl(5-isopropyl-2-furyl)carbinol:  ; b.p. 84–86° (2 mm.); d_{25}^{25} 0.9395; n_D^{25} 1.4669.[315]

Diphenyl(3,4,5-triphenyl-2-furyl)carbinol:  ; m.p. 179°; from 3,4,5-triphenyl-2-furyl phenyl ketone and phenylmagnesium bromide.[337, 324] Was converted to the corresponding **chloride** (no constants), and thence to the **methyl ether,** m.p. 204°. Reduction gives rise to diphenyl(3,4,5-triphenyl-2-furyl)methane.[324]

Furylalkenols and Other Unsaturated Alcohols

3-(2-Furyl)allyl alcohol: [3-(2-furyl)-2-propen-1-ol]; C_4H_3O—CH=CHCH$_2$OH; b.p. 85–87° (4 mm.), 108–110° (4 mm.), 118–120° (18 mm.); d_{20}^{20} 1.1439, d_4^{17} 1.1008, d_4^{25} 1.1074; n_D^{17} 1.5494, n_D^{25} 1.5518, n_D^{27} 1.5520; **α-naphthylurethan,** m.p. 93–94°; **acetate,** b.p. 127° (20 mm.); d_{20}^{20} 1.0987; n_D^{20} 1.5180. The alcohol was obtained by partial catalytic hydrogenation of 3-(2-furyl)acrolein[259, 260] (see also Chapter 15), and by reduction using powdered aluminum and aluminum ethoxide in alcoholic xylene.[338] On distillation, it decomposes to some extent, and invariably leaves a high boiling residue. On standing it turns yellow, then red, and finally thickens.[259] **3-(2-Furyl)allylamine,** no constants, has been obtained by reduction of furylacrolein oxime with sodium and alcohol[178] (see also [266]). The following unsaturated alcohols, I, related to furyl-

[335] Hunsdiecker and Wirth, *Ber.*, **75,** 460 (1942).

[336] Hoehn and Murbach, *J. Am. Chem. Soc.*, **72,** 4323 (1950).

[337] Pütter and Dilthey, *J. prakt. Chem.*, **149,** 183 (1937).

[338] Likhosherstov, Arsenyuk, Zeberg and Karitskaya, *Zhur. Obshchei Khim., J. Gen. Chem.*, **20,** 627 (1950); *C. A.*, **44,** 7823 (1950).

allyl alcohol, were prepared by the action of appropriate Grignard reagents on 3-(2-furyl)acrylic ester[339] (see also p. 624).

$$C_4H_3O{-}CH{=}CHCOOEt \xrightarrow{RMgX} \underset{\textbf{I}}{C_4H_3O{-}CH{=}CHC(OH)R_2}$$

ALCOHOLS OF TYPE I:

R	b.p. (°C.)	b.p. (°C.) benzoic ester
C_2H_5	125 (16 mm.)	193 (11 mm.)
n-C_3H_7	130 (16 mm.)	198 (12 mm.)
i-C_4H_9	143 (17 mm.)	210 (18 mm.)
i-C_5H_{11}	174 (12 mm.)	224 (8 mm.)
C_6H_5	m.p. 59	—

In the same way, **3-(2-furyl)-1,1,2-triphenyl-2-propen-1-ol,** $C_4H_3O{-}CH{=}C(C_6H_5)C(OH)(C_6H_5)_2$, m.p. 175°; b.p. 248° (8 mm.), was obtained as one of the products formed by the interaction of 3-(2-furyl)-2-phenylacrylic ester and phenylmagnesium halide.[340]

Allylfurylcarbinol: [1-(2-furyl)-3-buten-1-ol]; $C_4H_3O{-}CH(OH)CH_2CH{=}CH_2$; b.p. 96–97° (21 mm.), 266–272 (760 mm.); $d_4^{20.5}$ 1.0424; n_D 1.4919. Prepared from furfural by the action of allylmagnesium bromide.[341, 342]

Ethynylfurylcarbinol: [1-(2-furyl)-2-propyn-1-ol]; $C_4H_3O{-}CH(OH)C{\equiv}CH$; b.p. 69–70° (0.3 mm.), 83–85° (2 mm.); n_D^{23} 1.5056. Prepared in 65 per cent yield by the action of sodium acetylide on furfural in liquid ammonia[343] (see also [344]). More recently, Cymerman and Wilks[345] obtained it (21.5 per cent yield) by a similar synthesis starting with furfural sodium bisulfite in place of the free aldehyde.

(Phenylethynyl)furylcarbinol: [1-(2-furyl)-3-phenyl-2-propyn-1-ol]; $C_4H_3O{-}CH(OH)C{\equiv}CC_6H_5$; b.p. 186–187° (12 mm.); d_0 1.1601; from furfural and sodium phenylacetylide.[346, 347]

(1-Octynyl)furylcarbinol: [1-(2-furyl)-2-nonyn-1-ol]; $C_4H_3O{-}CH(OH)C{\equiv}C(CH_2)_5{-}CH_3$; b.p. 163° (13 mm.); d_0 1.004; from furfural and sodium n-hexylacetylide.[346, 347]

(Vinylethynyl)furylcarbinol: [1-(2-furyl)-4-penten-2-yn-1-ol]; $C_4H_3O{-}CH(OH)C{\equiv}CCH{=}CH_2$; b.p. 84–85° (2 mm.); d_4^{20} 1.0913; n_D^{20} 1.5380; from furfural and vinylethynylmagnesium bromide[295a] (see also [348]). Reduction with a copper-zinc couple gives furylbutadienylcarbinol, b.p. 83–84° (2 mm.); d_4^{20} 1.0770; n_D^{20} 1.5360[295a]; catalytically with hydrogen over platinum gives butylfurylcarbinol[295a].

1-(2-Furyl)-3-methyl-1-penten-4-yn-3-ol: $C_4H_3O{-}CH{=}CHC(OH)(CH_3)C{\equiv}CH$; b.p. 97° (3.5 mm.); n_D^{20} 1.5418; freezes > 5°. Obtained in high yield when furfur-

[339] Maxim and Georgescue, *Bull. soc. chim.*, [5] **3**, 2266 (1936).
[340] Maxim and Stancovici, *Bull. soc. chim.*, [5] **3**, 1319 (1936).
[341] Jaworsky, *Ber.*, **42**, 435 (1909).
[342] Sementzov and Konyukhov-Dobrinya, *J. Russ. Phys. Chem. Soc.*, **43**, 990 (1911); *C. A.*, **6**, 481 (1912).
[343] Jones and McCombie, *J. Chem. Soc.*, **1942**, 733.
[344] Macallum (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,125,384 (1938); *C. A.*, **32**, 7480 (1938).
[345] Cymerman and Wilks, *J. Chem. Soc.*, **1950**, 1208.
[346] Moureu and Desmots, *Compt. rend.*, **134**, 355 (1902).
[347] Moureu and Desmots, *Bull. soc. chim.*, [3] **27**, 370 (1902).
[348] Nazarov and Elizarov, *Bull. acad. sci. U.R.S.S. Classe sci. chim.*, **1940**, 189; *C. A.*, **36**, 741 (1942).

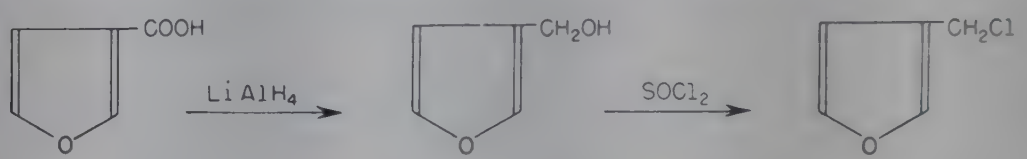
ylideneacetone is placed in reaction with lithium or calcium acetylide in liquid ammonia.[349]

1,8-Di(2-furyl)-3,6-dimethyl-1,7-octadien-4-yn-3,6-diol: $[C_4H_3O{-}CH{=}CHC(OH)(CH_3)C{\equiv}]_2$; b.p. 104–106° (10 mm.); **diacetate,** b.p. 99–101° (10 mm.); d_4^{24} 0.8771. The diol was derived from furfurylideneacetone and acetylenebismagnesium bromide.[350]

3-Furylcarbinol and Related Products

3-Furylcarbinol and Its Derivatives

Recently, 3-furylcarbinol (3-furylmethyl alcohol) was synthesized for the first time by Sherman and Amstutz[333] in 90 per cent yield by reduction of 3-furoic acid with lithium aluminum hydride. It is a colorless liquid, soluble



in water and in the common organic solvents, b.p. 54–55° (2 mm.), 79–80° (17 mm.); d_4^{20} 1.1391; n_D^{20} 1.4842; phenylurethan, m.p. 105.2–105.6°; α-naphthylurethan, m.p. 118.4–118.7°. It is more stable toward mineral acids than the isomeric 2-furylcarbinol (furfuryl alcohol), and may be converted into the corresponding chloride by the action of thionyl chloride in ethereal pyridine. Under these conditions, pure 3-furylmethyl chloride is isolable in approximately 50 per cent yield as a water-white liquid, b.p. 42–43° (17 mm.), 51–52° (27 mm.); d_4^{20} 1.1855; n_D^{20} 1.4863; 3-furylmethylisothiouronium picrate, m.p. 142–143°.

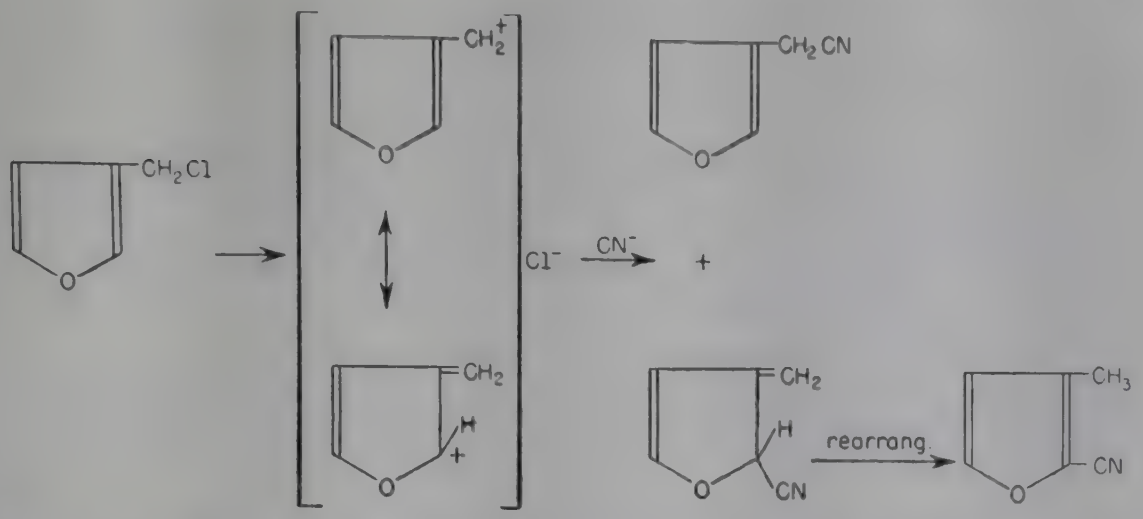
The chemical behavior of the chloride is as interesting as that of the α-isomer, furfuryl chloride. That is, both give rise to "abnormal" or allylic reaction products in addition to the normal metathetical products when treated with aqueous potassium cyanide. However, the ratio is quite different. Whereas furfuryl chloride is converted into a mixture of 5-methyl-2-furonitrile (abnormal product) and 2-furylacetonitrile (normal product) in a ratio *ca.* 85:15, 3-furylmethyl chloride gives 3-methyl-2-furonitrile (abnormal product) and 3-furylacetonitrile (normal product) in a ratio *ca.* 10:90.[o] The latter reaction is subject to a similar interpretation to that given elsewhere[p] to account for the behavior of furfuryl chloride.

[o] The nitriles were difficult of separation by distillation, hence they were converted directly to the corresponding carboxylic acids which were isolated in the ratio indicated above.[333]

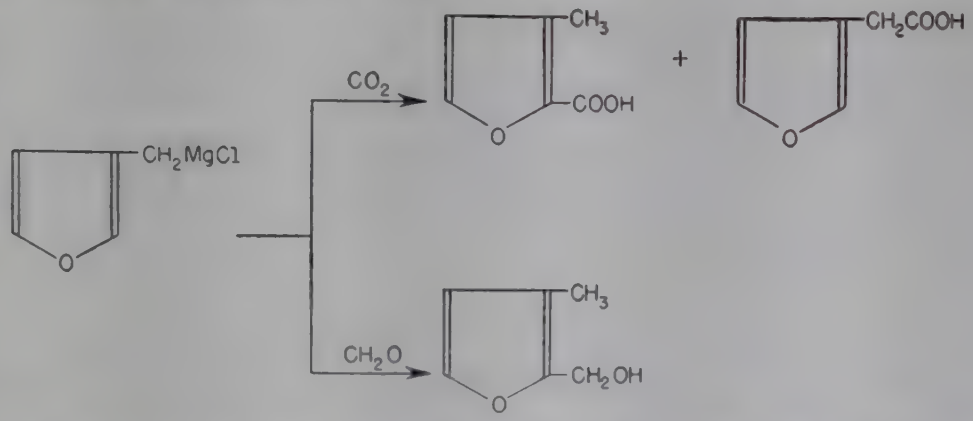
[p] For discussion of this reaction, see p. 550.

[349] Oroshnik and Mebane, *J. Am. Chem. Soc.*, **71**, 2062 (1949).

[350] Yasnopol'skii, *Zhur. Obshchei Khim, J. Gen. Chem.*, **19**, 300 (1949); *C. A.*, **43**, 6573 (1949).



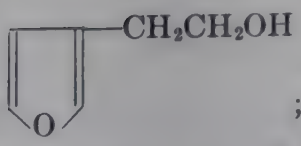
From 3-furylmethyl chloride and magnesium, in ether, a Grignard reagent is formed in approximately 70 per cent yield.[333] This is in contrast to the reported failure to obtain a "usable" Grignard reagent from furfuryl chloride (p. 232), an unfortunate circumstance which prevents comparison of the properties of the two isomers. 3-Furylmethylmagnesium chloride, in two separate reactions, gave rise to large amounts of "abnormal" products. Thus, carbonation produced a mixture of 3-methyl-2-furoic acid and 3-furylacetic acid in a ratio *ca.* 90:10; with formaldehyde, there was isolated only the allylic reaction product, 3-methylfurfuryl alcohol (3-methyl-



2-furyl)carbinol, in 33 per cent yield. It is interesting to compare this behavior with that of the Grignard reagent derived from the benzene analog, benzyl chloride. Carbonation of benzylmagnesium halide gives the normal product, phenylacetic acid; with formaldehyde, there is formed the product of allylic reaction, *o*-methylbenzyl alcohol.[351]

From such comparisons, Sherman and Amstutz[333] proposed the following relative order of decreasing tendency toward allylic reaction when the indicated halides are placed in reaction with aqueous, alkali cyanide: furfuryl, 3-furylmethyl, 3-thenyl, cinnamyl, benzyl. For the Grignard reagents, they proposed: cinnamyl, 3-furylmethyl, 3-thenyl, benzyl.

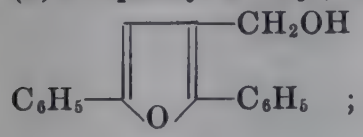
[351] Wheland, "Advanced Organic Chemistry," 2nd. Ed., p. 543, New York, John Wiley and Sons, Inc. (1949).

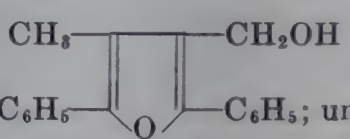
2-(3-Furyl)ethyl alcohol:  ; b.p. 64–65° (3 mm.), 89–90° (18 mm.); d_4^{20} 1.0941; n_D^{20} 1.4828; **phenylurethan,** m.p. 58.3–58.8°; **α-napthylurethan,** m.p. 85.2–85.9°. Obtained in 96.5 per cent yield by reduction of 3-furylacetic acid with lithium aluminum hydride.[333]

Miscellaneous 3-Furylcarbinols

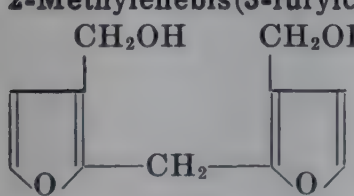
Primary Alcohols and Their Derivatives.

(2,5-Diphenyl-3-furyl)carbinol: [2,5-diphenyl-3-(hydroxymethyl)furan];

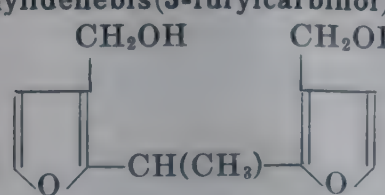
 ; m.p. 121–123°, 123–124°; by reduction of the corresponding aldehyde with aluminum isopropoxide in isopropyl alcohol.[352] Converted to the corresponding **chloride,** m.p. 62–63°, by the action of ethereal hydrogen chloride.[352] With morpholine, the chloride gave rise to 2,5-diphenyl-3-(N-morpholinomethyl)-furan (HCl salt, m.p. 217–221°)[352] (see also [353, 354, 355]). The following related 3-aminomethyl compounds were prepared by aminomethylation (the Mannich reaction) of 2,5-diphenylfuran: 3-(N-piperidinomethyl), m.p. 83–84°[356]; 3-dimethylaminomethyl, HCl salt, m.p. 217–220°[355] (see also [353]); 3-diethylaminomethyl, HCl salt, m.p. 177–179°.[355]

2,5-Diphenyl-4-methyl-3-furylcarbinol:  ; unknown. The corresponding **bromide,** m.p. 83–84°, was obtained by bromomethylation of 2,5-diphenyl-3-methylfuran.[356] With morpholine, in ether, the bromide was converted into 2,5-diphenyl-4-methyl-3-(N-morpholinomethyl)furan, m.p. 99–100°, which was also derived from appropriate straight chain compounds by ring closure.[356]

2-Methylenebis(3-furylcarbinol): [3,3′-bishydroxymethyl-2,2′-difurylmethane];

 ; **internal ether,** m.p. 128°. By the action of formaldehyde on ethyl furoate in cold, concentrated sulfuric acid, and subsequent saponification and decarboxylation[76] (see also p. 506).

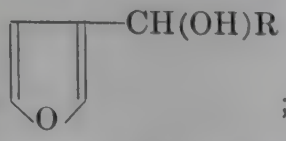
2-Ethylidenebis(3-furylcarbinol): [3,3′-bishydroxymethyl-2,2′-difurylmethylmethane];

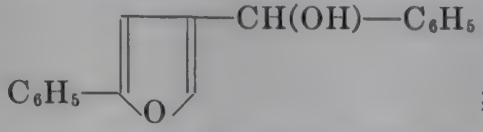
 ; **internal ether,** b.p. 133° (11 mm.); prepared as in above preparation but using acetaldehyde in place of formaldehyde.[76]

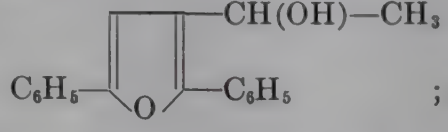
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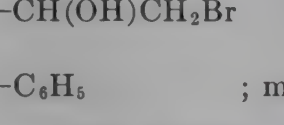
[352] Bailey and Lutz, *J. Am. Chem. Soc.*, **67**, 2232 (1945).
[353] Lutz and Bailey, *J. Am. Chem. Soc.*, **67**, 2229 (1945).
[354] Lutz and Bailey, *J. Am. Chem. Soc.*, **68**, 2002 (1946).
[355] Bailey and Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).
[356] Bailey and Nowlin, *J. Am. Chem. Soc.*, **71**, 732 (1949).

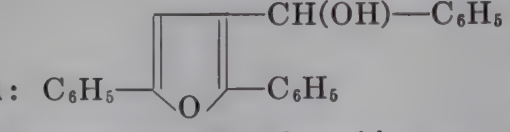
Secondary Alcohols and Their Derivatives.

Alkyl-3-furylcarbinols:  ; several of these types (R = CH_3, C_2H_5, C_3H_7) were prepared by treating 3-furaldehyde with the appropriate Grignard reagent.[279] Unfortunately, only the abstract is available and no constants are reported.

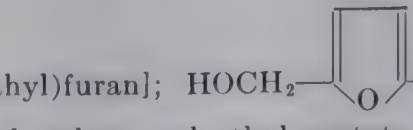
Phenyl(5-phenyl-3-furyl)carbinol:  ; m.p. 128.1–129.1°; **benzoate,** m.p. 123.1–124.1°; ***p*-nitrobenzoate,** m.p. 109.5–109.8°; by catalytic hydrogenation of 5-phenyl-3-benzoylfuran.[357]

Methyl(2,5-diphenyl-3-furyl)carbinol:  ; no constants; prepared by reduction of 2,5-diphenyl-3-furyl methyl ketone with aluminum isopropoxide in isopropyl alcohol.[358] Converted to the corresponding **chloride,** m.p. 63–64°, by the action of ethereal hydrogen chloride.[358] Reaction of the chloride with morpholine gave rise to 2,5-diphenyl-3-(1′-N-morpholinoethyl)furan (picrate, m.p. 173–175°), which underwent oxidative cleavage to 1,2-dibenzoyl-3-N-morpholino-1-butene when treated with nitric acid in glacial acetic acid.[358]

Bromomethyl(2,5-diphenyl-3-furyl)carbinol: [3-(2-bromo-1-hydroxyethyl)-2,5-diphenylfuran];  ; m.p. 124–126°; by reduction of 3-bromoacetyl-2,5-diphenylfuran with aluminum isopropoxide. With morpholine it gives rise to **N-morpholinomethyl(2,5-diphenyl-3-furyl)carbinol,** HCl salt, m.p. 202–203°.[359]

Phenyl(2,5-diphenyl-3-furyl)carbinol:  ; m.p. 105°; **acetate,** m.p. 84°; by hydrolysis of the corresponding bromide, m.p. 110°, which was obtained by the action of hydrogen bromide, in glacial acetic acid, on 1,2-dibenzoyl-3-phenylcyclopropane.[360]

Furandialkanols

2,5-Furandimethanol: [2,5-bis(hydroxymethyl)furan];  ; m.p. 75.5–77°, 80°; soluble in water, alcohol, ether, and ethyl acetate. Obtained from 5-hydroxymethylfurfural by the Cannizzaro reaction,[361, 362] and by hydrogena-

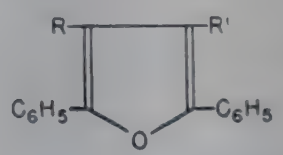
[357] Fuson, Fleming and Johnson, *J. Am. Chem. Soc.*, **60,** 1994 (1938).
[358] Bailey and Hakki, *J. Am. Chem. Soc.*, **71,** 2886 (1949).
[359] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70,** 1359 (1948).
[360] Kohler and Jones, *J. Am. Chem. Soc.*, **41,** 1249 (1919).
[361] Blanksma, *Rec. trav. chim.*, **29,** 403 (1910).
[362] Middendorp, *Rec. trav. chim.*, **38,** 1 (1919).

tion over Raney nickel.[363] **Diacetate,** m.p. 64°.[361] **Dibenzoate,** m.p. 76–77°.[363] **Ethers:** monomethyl, b.p. 132–134° (23 mm.); $n_D^{16.5}$ 1.4860; monoethyl, b.p. 152–157° (20 mm.); n_D^{15} 1.4865; from the corresponding 5-alkoxymethylfurfurals by the Cannizzaro reaction.[362] **Amine derivatives:** 5-(N,N-dimethylaminomethyl)furfuryl alcohol, $(CH_3)_2NCH_2—C=CHCH=C—CH_2OH$ (O), b.p. 110–111° (3 mm.); d_{25} 1.07; n_D^{25} 1.4968; hydrochloride, m.p. 120–121°, by condensation of furfuryl alcohol with formaldehyde and dimethylamine hydrochloride;[77] 5-(N-morpholinomethyl)furfuryl alcohol, b.p. 128–130° (1 mm.); d_{30} 1.12; n_D^{25} 1.5195; (hydrochloride, m.p. 136–136.5°)[77]; 2,5-bis(N,N-dimethylaminomethyl)furan $(CH_3)_2NCH_2—C=CHCH=C—CH_2N(CH_3)_2$ (O), b.p. 107–109° (10 mm.); n_D^{20} 1.4728; picrate, m.p. 202–205°; by condensation of furfuryldimethylamine with formaldehyde and dimethylamine in acetic acid.[78]

2,5-Furanbis(dibenzylmethanol): $(C_6H_5CH_2)_2C(OH)$—(O)—$C(OH)(C_6H_5CH_2)_2$; b.p. 193–195° (30 mm.); d_{27} 1.126; by the action of benzylmagnesium chloride on 2,5-furandicarboxylic ester.[276]

2,5-Furanbis(diphenylmethanol): $(C_6H_5)_2C(OH)$—(O)—$C(OH)(C_6H_5)_2$; m.p. 165.5°; from 2,5-furandicarboxylic ester and phenylmagnesium bromide. **Ethers:** dimethyl, m.p. 88.2°; diethyl, m.p. 171°.[276]

2,5-Diphenylfuran-3,4-dimethanol: [2,5-diphenyl-3,4-bis(hydroxymethyl)furan]. Structure shown below, where R = R′ = CH_2OH. The dihydroxy compound itself has not been reported, but the corresponding bischloromethyl derivative, m.p. 145–147°, was obtained by the action of anhydrous hydrogen chloride and formaldehyde on 2,5-diphenylfuran.[354] The following related compounds have been described:



R	R′	Physical constants (°C.)	Ref.
$HOCH_2$—	$C_6H_{11}N—CH_2$—	m.p. 169–170	356
$HOCH_2$—	$C_4H_8ON—CH_2$—	m.p. 176–177	355, 354
		acetate, m.p. 187–188	
		benzoate, m.p. 183–185	
$ClCH_2$—	$C_4H_8ON—CH_2$—	m.p. 232–233	356
$BrCH_2$—	$C_4H_8ON—CH_2$—	m.p. 215–217	354
		HCl salts, m.p. (°C.)	
$(CH_3)_2N—CH_2$—	R	297–298	354
$(C_2H_5)_2N—CH_2$—	R	239–240	354
$C_6H_{11}N—CH_2$—	R	246–247	354
$C_4H_8ON—CH_2$—	R	143–145, 241–245	354, 354

[363] Newth and Wiggins, *Research (London)*, **3**, Suppl. 50–1 (1950); *C. A.*, **44**, 68[illegible] (1950).

Nitro and Amino Alcohols

α-Nitro alcohols, I, have been obtained together with the corresponding furylnitroölefins, II, by condensation of furfural with nitroparaffins in the presence of potassium bicarbonate or carbonate.[364] They are yellow, unstable liquids of fragrant odor and sweet taste, and physiologically, they have a mydriatic action, the intensity of which is inversely proportional to the number of carbon atoms in the side chain. Reduction of I with zinc dust in acetic acid gives rise to α-amino alcohols, III, which by condensation with aldehydes and subsequent reduction of the aldimine, or by alkylation according to standard procedures, are transformed into the appropriate alcohols containing *sec.*- and *tert.*-amino groups, IV and V, respectively.[364, 365] Related types have also been obtained by reduction of aminoalkyl furyl ketones[366, 367] (see also p. 436). Reduction of the oximes of furoin (VI, R

$$C_4H_3O{-}CHO + RCH_2NO_2 \xrightarrow{(KHCO_3)}$$

$$C_4H_3O{-}CH(OH)CH(NO_2)R \quad (I) \qquad + \qquad C_4H_3O{-}CH{=}C(NO_2)R \quad (II)$$

$$\downarrow (H)$$

$$C_4H_3O{-}CH(OH)CH(NH_2)R \quad (III) \xrightarrow{R'X} C_4H_3O{-}CH(OH)CH(NR'R')R \quad (V)$$

$$\downarrow R'CHO$$

$$C_4H_3O{-}CH(OH)CH(N{=}CHR')R \xrightarrow{(H)} C_4H_3O{-}CH(OH)CH(NHR')R \quad (IV)$$

Table 7. α-Nitroalkanols[364]

$C_4H_3O{-}CH(OH)C(NO_2)RR'$

Compound	Physical constants		
	b.p. (°C.)	d_4^{20}	n_D^{20}
1-Furyl-2-nitro-1-ethanol	130–131 (7.5 mm.)	d_4^0 1.3122	1.5156
methyl ether	109 (9 mm.)	1.2079	1.4836
ethyl ether	105 (9 mm.)	d_4^0 1.1617	1.4785
1-Furyl-2-nitro-1-propanol	126 (7 mm.)	1.2455	1.5039
methyl ether	113 (13 mm.)	1.1606	1.4766
1-Furyl-2-methyl-2-nitro-1-propanol	130.5–131 (9 mm.)	1.2104	1.4921
1-Furyl-2-nitro-1-butanol	150–151 (16 mm.)	1.1938	1.4951
1-Furyl-2-nitro-1-pentanol	126–127 (6 mm.)	1.1392	1.4840
1-Furyl-3-methyl-2-nitro-1-butanol	146–147 (16 mm.)	1.1470	1.4874
1-Furyl-4-methyl-2-nitro-1-pentanol	133 (15 mm.)	—	—

TABLE 8. α-AMINOALKANOLS

Compound	Physical constants (°C.)	Derivatives, m.p. °C.	Ref.
1-Furyl-2-aminoethanol	m.p. 89	hydrochloride, 117 oxalate, 199 O,N-dibenzoate, 146 methyl ether: b.p. 77 (9 mm.) d_4^{20} 1.0650 n_D^{20} 1.4788	364
1-Furyl-2-(N-furfurylamino)-ethanol	b.p. 184–185 (18 mm.) d_4^{20} 1.1759 n_D^{20} 1.5312	—	364
1-Furyl-2-(N-piperidino)-ethanol	b.p. 127–128 (5 mm.)	hydrochloride, 172–174	366
1-Furyl-2-(N-4-methyl-piperidino)ethanol	b.p. 126–128 (4 mm.)	hydrochloride, 70–72 (dec.)	366
1-Furyl-2-(N-morpholino)-ethanol	m.p. 67–68 b.p. 146–150 (5 mm.)	hydrochloride, 185–186 (dec.)	366
1,2-Difuryl-2-aminoethanol	m.p. 104–105	hydrochloride, 185 acid oxalate, 178	368
1-Furyl-2-phenyl-2-amino-ethanol	m.p. 123	N-furfurylidene, 119	368
1-Phenyl-2-furyl-2-amino-ethanol	m.p. 106–107	—	368
1-Furyl-2-amino-1-propanol	b.p. 109 (7 mm.) d_4^{20} 1.1208 n_D^{20} 1.5068	hydrochloride, *ca.* 130 oxalate, 215 (dec.)	364
1-Furyl-2-(N-methylamino)-1-propanol	—	hydrochloride, 130	372
1-Furyl-2-(N-furfurylamino)-1-propanol	m.p. 88–88.5 b.p. 150 (6 mm.)	hydrochloride, 168 oxalate, 167	364, 365
1-Furyl-2-(N-benzylamino)-1-propanol	m.p. 92	hydrochloride, 160 oxalate, 181 (dec.)	364, 365
1-Furyl-2-(N,N-diethyl-amino)-1-propanol	b.p. 123 (12 mm.) d_4^{20} 0.9895 n_D^{20} 1.4747	hydrochloride, 147–148 ethiodide, 176	364
1-Furyl-2-methyl-2-amino-1-propanol	b.p. 119–120 (14 mm.) d_4^{20} 1.0894 n_D^{20} 1.5020	—	364
1-Furyl-2-amino-1-butanol	m.p. 63 b.p. 137–138 (16 mm.)	hydrochloride, 140 oxalate, 202 (dec.)	364
1-Furyl-2-(N-furfurylamino)-1-butanol	m.p. 76–76.5	—	364
1-Furyl-3-methyl-2-amino-1-butanol	b.p. 125–126 (8 mm.) d_4^{20} 1.0663 n_D^{20} 1.4983	hydrochloride, 145 oxalate, 218	364
1-Furyl-3-methyl-2-(N-furfurylamino)-1-butanol	b.p. 156–157 (8 mm.)	—	364

TABLE 8—*Continued*

Compound	Physical constants (°C.)	Derivatives m.p. °C.	Ref.
1-Furyl-2-amino-1-pentanol	b.p 128–129 (6 mm.) d_4^{20} 1.0537 n_D^{20} 1.4920	—	364
1-Furyl-2-(N-furfurylamino)-1-pentanol	b.p. 159–163 (6 mm.)	—	364
1-Furyl-4-methyl-2-amino-1-pentanol	b.p. 124 (7 mm.) d_4^{20} 1.0293 n_D^{20} 1.4889	—	364

= C_4H_3O) and furobenzoin (VI, R = C_6H_5) gives the appropriately substituted hydroxyalkylamines, VII.[368] Isomeric with VII (R = C_6H_5) is 1-furyl-2-phenyl-2-aminoethanol, VIII, which was obtained, in low yield, from furfural and N-benzylideneaminoacetic acid according to the simplified reaction scheme illustrated below. For a discussion of the diastereoisomerism of these types, see Lespagnol and van Thienen.[368]

$$C_4H_3O{-}CO{-}CH(OH)R \xrightarrow{NH_2OH} \xrightarrow{(H)} C_4H_3O{-}CH(NH_2){-}CH(OH)R$$

VI VII

$$C_6H_5{-}CH{=}NCH_2COOH \rightleftharpoons C_6H_5{-}CH_2N{=}CHCOOH \xrightarrow{C_4H_3O{-}CHO}$$

$$C_4H_3O{-}CH(OH)CH(N{=}CHCOOH)C_6H_5 \xrightarrow{HOH}$$

$$C_4H_3O{-}CH(OH)CH(NH_2)C_6H_5$$

VIII

Furyl(3-N,N-dimethylaminopropyl)carbinol: $C_4H_3O{-}CH(OH)CH_2CH_2CH_2N(C_2H_5)_2$; b.p. 88° (0.07 mm.); from furfural and 3-(N,N-diethylamino)propylmagnesium chloride. Reported to be useful as a therapeutic agent, or for the preparation of such agents.[369, 370, 371]

[364] Kanao, *J. Pharm. Soc. Japan*, **550**, 1019 (1927); *C. A.*, **22**, 1588 (1928).
[365] Kanao, *J. Pharm. Soc. Japan*, **50**, 24 (1930); *C. A.*, **24**, 1856 (1930).
[366] Burger and Harnest, *J. Am. Chem. Soc.*, **65**, 2382 (1943).
[367] Burger, (to Smith, Kline and French Laboratories), U. S. Pat. 2,400,913 (1946); *C. A.*, **40**, 5455 (1946).
[368] Lespagnol and van Thienen, *Bull. sci. pharmacol.*, **45**, 49 (1938).
[369] Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).
[370] Miescher and Marxer (to Ciba Pharmaceutical Products, Inc.), U. S. Pat. 2,411,664 (1946); *C. A.*, **41**, 6276 (1947).
[371] Soc. pour l'ind. chim. à Bâle, Brit. Pat. 565,745 (1944); *C. A.*, **40**, 5534 (1946).
[372] Hildebrandt and Klavehn (Knoll A.-G. chem. Fab.), Ger. Pat. 585,667 (1933); *C. A.*, **28**, 1355 (1934).

Chapter 8

FURFURAL—PRODUCTION, ANALYTICAL METHODS AND PHYSICAL PROPERTIES

Historical and Industrial Development

In 1832, Dobereiner[1] reported the isolation of a few drops of a yellow oil from the milky distillate obtained incident to the preparation of formic acid from sugar by the action of manganese dioxide and sulfuric acid. The quantity of this oil, later to be called furfural, was too small for characterization, and Dobereiner assigned to it the fanciful name of "artificial oil of ants."

While 1832 has usually been considered to mark the discovery of furfural, it appears that Dobereiner first obtained it approximately eleven years prior to his published report. Thus, in 1849, he states[2] that the "oil" was noted 28 years previously. In confirmation is a remark by his contemporary, Stenhouse, who in 1850 wrote, "Nearly 30 years ago, Dobereiner first observed . . ."[3] The agreement between these two statements must be accepted as establishing the year 1821 as the birth-year of furfural.

The next mention of the new product was made by an American chemist, Emmet, working at the University of Virginia.[4] In preparing formic acid from sugar, and also from rye and corn, Emmet found the inclusion of manganese dioxide to be unnecessary; to be, in fact, somewhat objectionable. He also observed sulfuric acid to be the preferred reagent, while noting that it could be replaced by phosphoric acid or zinc chloride. In describing his experiments, he says:

"During the preparation of formic acid by Dobereiner's process, as well as my own in which no peroxide of manganese is employed, there is always formed, previous to carbonization, a considerable quantity of vegetable oil which, at first, might be considered as arising from the excess of hydrogen and carbon in the process; but a special inquiry has convinced me that this is not the case, although the oil is so abundant that it may actually be observed floating in drops down the neck of the retort. When the sulfuric acid is so far diluted as not to carbonize the mixture, at the heat of boiling water, little else than this spicy oil passes over by distillation; but as soon as the matter becomes black, its formation ceases, and if we begin at once with sulfuric acid about one-half diluted it does not appear at all; but instead of it, strong formic acid, without any foreign odor and quite colorless. This volatile oil would

[1] Dobereiner, *Ann.*, **3**, 141 (1832).
[2] Dobereiner, *J. prakt. Chem.*, **46**, 167 (1849).
[3] Stenhouse, *Phil. Mag.*, **37**, 226 (1850).
[4] Emmet, in *J. prakt. Chem.*, **12**, 120 (1837); *Ann.*, **28**, 249 (1839).

not be regarded as objectionable by many, since it imparts an aroma like that of cassia or cinnamon, and a taste somewhat similar to that produced by hydrocyanic acid."

The "oil" of Emmet, having the odor of cassia, was evidently the "oil" of Dobereiner, and Emmet appears to have established that it could be obtained from most vegetable substances. This was later confirmed by Stenhouse[5] who made an extensive study of the "oil," obtained from "grain of any kind, sawdust, husks of corn, and oat meal." Stenhouse was the first to recognize the volatility of the product with steam as a means of purification. Upon distilling a mixture of the "oil" and water, he observed that the organic product came over with the first 20–25 per cent of the distillate. From twelve pounds of oat meal[a] he was able to isolate one ounce of furfural by a process which he described in the following way:

"Take equal weights of oatmeal (or sawdust) and sulfuric acid, dilute with its own bulk of water, introduce into a large copper still. When the mixture has boiled for some time, and the meal is quite charred, pour back the liquid which has distilled adding the same quantity of water as at first, and distill almost to dryness. The liquid which passes over into the receiver is slightly milky owing to the presence of the 'oil,' and at the same time strongly acid from sulfurous and formic acids which it contains. It is neutralized with slaked lime which produces a deep yellow color, and again distilled until about one-fifth to one-fourth is taken over. The distillate is mixed with a considerable quantity of fused calcium chloride, and again distilled. The calcium chloride retains a great part of the water in which the 'oil' is moderately soluble. If too much water passes over after the second distillation, more calcium chloride is added, and a third distillation is carried out. The 'oil' comes over mixed with a little water, and sinks to the bottom of the receiver."

The product described by Stenhouse was almost colorless when freshly prepared, but was observed to darken on standing. The boiling point was reported to be 168°, and the specific gravity 1.1006 at 27°. The latter value suggests that Stenhouse's furfural was incompletely freed from water, but on the basis of his analytical results, he was able to assign the correct formula, $C_5H_4O_2$.

Somewhat later, Stenhouse[3] speculated on the nature of vegetative materials which give rise to furfural on treatment with sulfuric acid. He proposed that, under such conditions, all plant materials would produce furfural or some related product, and to test this theory, he investigated the products derived from certain sea weeds. A liquid, later[6, 7, 8] identified

[a] Presumably Stenhouse worked with ground whole oats, and not with what we, today, call oatmeal.

[5] Stenhouse, *Phil. Mag.*, **18**, 122 (1840); *Ann.*, **35**, 301 (1840).

[6] Maquenne, *Compt. rend.*, **109**, 571, 603 (1889).

[7] Bieler and Tollens, *Ber.*, **22**, 3062 (1889).

[8] Bieler and Tollens, *Ann.*, **258**, 110 (1890).

as a mixture of furfural and 5-methylfurfural, was obtained which Stenhouse named "fucusole" after the botanical name of the sea weed, fucus. His final conclusion was that the "matière incrustante" of all phanerogamous plants yields furfural; that algae, mosses and lichens produce "fucusole," whereas ferns give rise to a different, but related product.

We are indebted to Fownes[9] for the name furfural. Actually, he proposed the name "furfurol" (furfur-bran; oleum-oil) for the product which he derived from bran and aqueous sulfuric acid, but in America the suffix "ol" has been changed to "al" in recognition of the aldehydic nature of the compound. Fownes confirmed the empirical formula first offered by Stenhouse, and recorded the properties as follows[10]:

"When free from water, and freshly rectified, it is nearly colorless, but after a few hours standing it acquires a brownish tint which eventually deepens almost to blackness. When in contact with water, or when not properly rendered anhydrous, it is less subject to change, and merely assumes a yellow color.[b] Its odor resembles that of a mixture of bitter almond oil and oil of cassia, but has less fragrance. Its specific gravity is 1.168 at 60°F., and its boiling point, 323°F. It distills at that temperature without alteration. It dissolves to a large extent in cold water, and also in alcohol. Its solution in concentrated sulfuric acid has a magnificent purple color, and is decomposed by water. Nitric acid, with the aid of heat, attacks the oil with prodigious violence, evolving copious red fumes and generating oxalic acid which appears to be the sole product. It dissolves in a solution of potassium hydroxide forming a deep brown liquid from which acid precipitates a resinous mass. With slight heat, it explodes when acted upon by metallic potassium."

Fownes also observed that furfural reacted with ammonia to form "furfural amide," now called hydrofuramide, and he prepared an isomer of this compound which he called furfurin, as it is known today.

In 1849, Cahours[12] obtained 103 grams of furfural from 4 kg. of wheat bran, 3.2 kg. of sulfuric acid and 10 liters of water. He attempted to determine the particular constituent of the bran which gave rise to furfural, and was successful in proving that it did not have its origin in the starch, gluten, or lignin components. He was the first to note the similarity between benzaldehyde and furfural, and the first to prepare thiofurfural.

von Babo[13] attempted to improve the yield of furfural from bran by substituting zinc chloride for sulfuric acid. He employed 33–40 per cent of the salt based on the weight of bran, and reported the amount of water

[b] It is interesting to observe that this inhibiting action of water reported by Fownes receives confirmation approximately 100 years later in connection with its effect on the autoxidation of furfural, the reaction responsible for its discoloration in storage.[11]

[9] Fownes, *Ann.*, **54**, 52 (1845).
[10] Fownes, *Phil. Mag.*, **26**, 254 (1845).
[11] Dunlop, Stout and Swadesh, *Ind. Eng. Chem.*, **38**, 705 (1946).
[12] Cahours, *Ann.*, **69**, 82 (1849).
[13] von Babo, *Ann.*, **85**, 100 (1853).

to be immaterial. On distillation, which was continued until the residue charred, there was obtained in the distillate, water, furfural, hydrochloric acid, and finally, a fatty material which proved to be margaric acid. Six pounds of bran produced one to two ounces of furfural. Calcium chloride gave poor results, but von Babo suggested that improved yields might be possible if the digestion were conducted under pressure.

The work of von Babo, reported in 1853, may be considered to close the first stage in the development of furfural. In the years following, the new aldehyde was prepared many times, but already it was evident that it could be obtained from almost any vegetative material by the action of acidic materials in aqueous medium.

Although furfural was discovered in 1821, there was little interest in processes for producing it commercially or in its industrial potentialities until after the turn of the present century. However, between 1910 and the early twenties several patented processes appeared. Raisin[14] and Bergström[15] described methods for producing the aldehyde, along with methanol and acetic and formic acids, by treating sawdust with sulfurous acid at 150°. Lederer and Lederer[16] (see also [17]) called attention to the fact that the furfural formed on acid-hydrolysis of lignocellulosic materials interfered with subsequent fermentation of the glucose. They[16] (see also [18]) proposed to eliminate this difficulty, and also to effect recovery of furfural by distilling the hydrolyzed mass, below 80°, prior to the fermentation step. Heuser[19] steamed wood and straw at superatmospheric pressure, and reported a considerable quantity of the aldehyde in the distillate. From the same raw materials, Pringsheim[20] (see also [21]) was able to produce furfural by the action of hydrochloric acid vapors at 110–140°.

Patents were issued to Ricard[22] for the manufacture of furfural from cellulosic products, particularly kapok, using dilute acid and rapidly distilling the aldehyde from the reaction chamber during the period of its formation.

In this country, the impact of World War I crystallized a desire for national self-sufficiency which, among other things, focused a great deal of attention on the possible utilization of agricultural waste materials in

[14] Raisin, French Pat. 446,871 (1911); *C.A.*, **7**, 2835 (1913).
[15] Bergström, Swedish Pat. 40,842 (1916); *C.A.*, **10**, 2635 (1916).
[16] Lederer and Lederer, French Pat. 464,608 (1913); *C. A.*, **8**, 3364 (1914).
[17] Lüers, *Z. Spiritusind.*, **60**, 7 (1937).
[18] Classen, British Pat. 142,480 (1920); *C. A.*, **14**, 2645 (1920).
[19] Heuser, *Papier Ztg.*, **39**, 1280 (1914); *C. A.*, **8**, 2945 (1914); *Z. angew. Chem.*, **27**, 654 (1914); *C. A.*, **9**, 859 (1915).
[20] Pringsheim, *Cellulosechemie*, **2**, 123 (1921); *C. A.*, **16**, 2986 (1922).
[21] Meunier, French Pat. 523,807 (1917); *Compt. rend.*, **174**, 468 (1922).
[22] Ricard, U. S. Pat. 1,322,054 (1920); *C. A.*, **14**, 284 (1920); British Pat. 129,025 (1917); *C. A.*, **14**, 746 (1920); French Pat. 485,967 (1918); *C. A.*, **13**, 1863 (1919).

industrial processes. From then on progress in the industrial development of furfural was rapid. Especially noteworthy were the researches carried on in the National Bureau of Chemistry by LaForge, Mains and others. These investigations, concerned primarily with the utilization of corn cobs, resulted in processes for the manufacture of various products,[23] including furfural[24, 25] (see also [26]) and pentosan adhesive[27] from which furfural was obtainable by the action of sulfuric acid.[28] This work culminating in a pilot plant development by LaForge and Mains,[29] demonstrated the feasibility of producing furfural from corn cobs (see also [30]), although the economic analysis presented by these workers[31] was based on production figures which were not reached for at least another decade, and failed to take into account many essential items, such as development and maintainence costs and the like. Initially, high pressure steam alone was employed as the digestive agent, but it was later found to be beneficial to add a small amount of sulfuric acid to the raw material. The cob-acid mixture was digested with steam at 135 pounds pressure for approximately two hours, while distilling off the furfural as formed, and collecting it as a dilute aqueous solution. The basis for the economical recovery of the aldehyde from such solutions had been laid by the work of Mains[32] who exhaustively studied the characteristics of furfural-water systems (see p. 318).

At about the same time, The Quaker Oats Company, through the agency of its consultant, Carl S. Miner, and his associate, Harold J. Brownlee, independently developed the production of furfural from oat hulls, and in February, 1922, announced its availability in quantities of several tons per month. For the history of the development, the reader is referred to the papers of Miner, Trickey and Brownlee,[33] Killeffer,[34] Brownlee,[35] Peters,[36]

[23] LaForge and Hudson, *Ind. Eng. Chem.*, **10**, 925 (1918).
[24] LaForge, *Ind. Eng. Chem.*, **13**, 1024 (1921); **16**, 130 (1924).
[25] LaForge, Tooke, Mains and Clarke, British Pat. 207,116 (1923); *C. A.*, **18**, 1199 (1924).
[26] Dunlap and Fischlowitz, *Chem. & Met. Eng.*, **22**, 774 (1920).
[27] LaForge, *Chem. Age N. Y.*, **28**, 332 (1920).
[28] Monroe, *Ind. Eng. Chem.*, **13**, 133 (1921); U. S. Pat. 1,357,467 (1921); *C. A.*, **15**, 239 (1921).
[29] LaForge, *Ind. Eng. Chem.*, **15**, 499 (1923); LaForge and Mains, *Ibid.*, **15**, 823, 1057 (1923).
[30] Sweeney, *Iowa State Coll. Eng. Expt. Sta., Bull. No.* **73**, 7–11 (1924); *C. A.*, **19**, 3353 (1925).
[31] Mains and LaForge, *Ind. Eng. Chem.*, **16**, 356 (1924).
[32] (a) Mains, *Chem. & Met. Eng.*, **26**, 779 (1922); (b) *Ibid.*, **26**, 841 (1922); (c) *Ibid.*, **31**, 307 (1924).
[33] Miner, Trickey and Brownlee, *Chem. & Met. Eng.*, **27**, 299, 362 (1922).
[34] Killeffer, *Ind. Eng. Chem.*, **18**, 1217 (1926).
[35] Brownlee, *Ind. Eng. Chem.*, **19**, 422 (1927).
[36] Peters, *Ind. Eng. Chem.*, **28**, 755 (1936).

and Brownlee and Miner.[37] The selection of oat hulls as the raw material was a happy one, this source being continuously available in large tonnages throughout the year at The Quaker Oats Company mill in Cedar Rapids, Iowa. For many years this mill was the sole producer of furfural in commercial quantities, and the plant is in operation today with greatly expanded and modernized facilities. Additional production capacity in this country was provided during World War II by construction of a new and larger plant at Memphis, Tennessee,[38] and late in 1951, production was begun from the newest installation at Omaha, Nebraska. Smaller facilities are known to be in operation in Sweden, France and Italy. However, with expanding industrial markets, furfural has outgrown its original position as a by-product of the cereal industry, and while oat hulls are still being used, corn cobs are now the major source of the world's production of the aldehyde.

The producing process employed by The Quaker Oats Company involves the use of large spherical digesters which are charged with raw material and sulfuric acid, and rotated slowly while steam is introduced to bring the charge to a selected operating temperature. At this point, a vapor outlet valve is opened to permit removal of the formed furfural as a steam distillate which is led into a fractionating column. An enriched furfural-water distillate is withdrawn overhead, and further processed to obtain the furfural of commerce. By appropriate adjustment of operating temperature and/or acid concentration, the duration of the digestion cycle can be varied over rather wide limits. The technical details of the process form the subject matter of patents to Miner and Brownlee[39] and Brownlee,[40] and an excellent account of some of the many operating variables has been given by Brown, Symons and Wilson.[41]

The advent of furfural as an industrial chemical stimulated interest in its properties and potential applications,[36] and as new and larger uses were discovered, impetus was given to further development work on processes and raw materials which would permit yet more economical production of the aldehyde. These efforts, world-wide in scope, have continued more or less unabated, to the present time, and at this writing comprise a rather imposing segment of the chemical and patent literature. In general, two types of processes have been studied, which may be characterized as single-stage and multi-stage operations. In the former, hydrolysis of pentosan to pentose and conversion of the latter to furfural are carried out

[37] Brownlee and Miner, *Ind. Eng. Chem.*, **40**, 201 (1948).

[38] Anon., *Chem. & Met. Eng.*, **52**, 132 (1945).

[39] Miner and Brownlee (to The Quaker Oats Co.), U. S. Pat. 1,735,084 (1930); *C. A.*, **24**, 630 (1930); British Pat. 203,691 (1923); *C. A.*, **18**, 692 (1924).

[40] Brownlee (to The Quaker Oats Co.), U. S. Pat. 1,919,877 (1933); *C. A.*, **27**, 4819 (1933); U. S. Pat. 2,140,572 (1938); *C. A.*, **33**, 2541 (1939).

[41] Brown, Symons and Wilson, *J. Council Sci. Ind. Research*, **20**, 225 (1947).

simultaneously in a single digestion. The multi-stage process involves a preliminary mild hydrolysis of the raw material to solubilize the pentosan fraction without materially affecting the cellulose component, following which the pentose liquor is subjected to the more drastic conditions required for furfural formation. This latter type of operation is not employed industrially in this country at the present time, but has been the subject of many investigations both here and in Europe, notably in connection with pulping operations employing deciduous woods of high pentosan content. In a book of this type, concerned primarily with the chemistry of furan compounds, it would, of course, be out of place to enter into a detailed discussion of the technology of furfural production. For those interested in this subject there are the references already cited. Many others[42] have been grouped at the end of the chapter as reference 42, although no attempt has been made at completeness.

Sources

It is not within the scope of this monograph to enter into a detailed discussion of the composition of vegetative materials. However, a few remarks on this subject are considered necessary to an understanding of the technology of furfural.

In addition to cellulose, natural cellulose fibers contain hemicelluloses, polyuronic acids and lignin. Like cellulose, the hemicelluloses are composed of long chains built up from sugar units, largely the pentosans (xylan, araban) and hexosans (mannan, galactan), although they are by no means accurately defined.[43] Of these components, it is the pentosans which are the major precursors of furfural, but it will be shown later that this aldehyde may also be obtained from uronic acids, and patents have been granted claiming high yields from cellulose.

The pentosans are almost as widely distributed in nature as cellulose, although in less abundance. Cereal grasses and their products such as oat hulls, corn cobs and the like, constitute one large natural storehouse, wood and wood products another. The chief constituent of the pentosan fraction of these materials is xylan, and according to Browne,[44] xylan with a little araban accounts for 25–30 per cent of cereal straws and grains, approximately 15–25 per cent of deciduous woods, and 5–15 per cent of coniferous woods, based on the dry matter of these plants. Xylan is also found in relatively large quantities in bark, roots, bran of seeds and in many vegetable gums. In general, the pentosans are more easily hydrolyzed by acids (see p. 287), and are more readily soluble in alkali than is cellulose, so that

[42] See end of chapter.

[43] Norman, in Ott, "High Polymers," Vol. 5, p. 429, New York, Interscience Publishers, Inc. (1943).

[44] Browne, "Handbook of Sugar Analyses," New York, John Wiley and Sons (1912).

it is possible to effect a separation by these means. Thus a pentosan, predominantly xylan, can be isolated from most plant materials by treatment with aqueous alkali, and precipitation of the filtrate with alcohol[45] (see also [46]). The xylan is generally accompanied by a smaller proportion of araban, as is indicated in many published investigations; see, for example, Auernheimer, Wickerham and Schniepp.[47]

Acid hydrolysis of pentosans produces the simple pentoses (xylose and arabinose), which on further exposure, lose water with formation of furfural (p. 289). The conversion from pentosan to furfural[c] takes place with such ease that the standard analytical method for estimating the former is actually based on the quantity of furfural produced when materials containing these complex polysaccharides are subjected to aqueous hydrochloric acid under controlled conditions (p. 295). By proper regulation of acid strength and temperature it is, of course, possible to obtain the intermediate pentose sugars which, as such, are quite scarce in nature. As a matter of fact, it has been suggested from time to time that such a procedure involving isolation of pentose should or could economically precede the commercial production of furfural. However, this has never been done on a large scale in this country, where by far the greatest amount of development work has been concerned with the one-stage process.

While the formation of furfural is usually attributed to the decomposition of pentosans, there are numerous references in the literature indicating that it can be obtained from other components of vegetable products. Of these, only a few will be mentioned here. Thus, Preece[49] hydrolyzed boxwood and obtained a non-pentosan material from which furfural could be derived. Schorger[50] isolated a galactan from western larch which gave rise to furfural, but no pentosan. All hexose carbohydrate material (cellulose, starch, sucrose and glucose) appears to give a small amount of furfural upon distillation with hydrochloric acid.[44, 51, 52, 53, 54, 55, 56, 57, 58, 59] Oxycellulose be-

[c] Heuser[48] reports that preliminary treatment of xylan with dilute aqueous alkali prior to distillation with hydrochloric acid is productive of higher yields of furfural.

[45] Hurd and Currie, *J. Am. Chem. Soc.*, **55**, 1521 (1933).
[46] Brown and Lewis, *Iowa State Coll. J. Sci.*, **7**, 29 (1932).
[47] Auernheimer, Wickerham and Schniepp, *Anal. Chem.*, **20**, 876 (1948).
[48] Heuser, *J. prakt. Chem.*, **211**, 69 (1921).
[49] Preece, *Biochem. J.*, **25**, 1304 (1931).
[50] Schorger, *Ind. Eng. Chem.*, **9**, 556 (1917).
[51] Völckel, *Ann.*, **85**, 59 (1853).
[52] Schiff, *Ber.*, **20**, 540 (1887).
[53] Fischer, *Ann.*, **270**, 64 (1892).
[54] Vignon, *Compt. rend.*, **126**, 1355 (1898).
[55] von Leersum, *Beiträge zur chemischen Physiologie und Pathologie*, **5**, 511 (1904).
[56] Gellet, *Bull. assoc. chim. sucr. dist.*, **35**, 53 (1917); *C. A.*, **12**, 2703 (1918).
[57] Hibbert, Henderson, Johnsen, Mitscherling and Wise, *Ind. Eng. Chem.*, **15**, 748 (1923).
[58] Gardner, *J. Am. Chem. Soc.*, **67**, 2111 (1945).
[59] Hunter, Wright and Hibbert, *Ber.*, **71**, 734 (1938).

haves similarly, the yield of furfural varying with the manner of preparing the oxycellulose, and the source of the original cellulose.[60, 61]

Crude cellulose, as obtained by the Cross and Bevan chlorination method, likewise gives some furfural on treatment with acid. Apparently this conversion proceeds by way of intermediate formation of glucuronic acid, which Günther, de Chalmot and Tollens[62] (see also [63, 64, 65]) in 1892 demonstrated to be a furfural precursor. For the conversion of galacturonic acid to furfural, see Franken.[66] Pectins, which are now regarded as polyuronic acids, also produce furfural under similar conditions[67] (see also [68]). The uronic acids are readily decarboxylated on heating with dilute mineral acids with formation of a pentose, xylose or arabinose. Thus, in these instances, it is again the aldopentoses which are responsible for furfural formation.

$$\text{Pectin} \xrightarrow{\text{HOH}} \text{HOOC(CHOH)}_4\text{CHO} \downarrow -\text{CO}_2 \text{HOCH}_2\text{(CHOH)}_3\text{CHO} \xrightarrow{-3\text{HOH}} \text{C}_4\text{H}_3\text{O—CHO}$$

Ascorbic acid in plant and animal tissue can be transformed into furfural, and an analytical procedure for the acid is based on this reaction[69] (see also [70]).

It may interest some readers to mention some of the numerous reports dealing with the occurrence or formation of furfural in natural oils, including camphor,[71, 72] citronella,[73] sassafras,[74] lavender[75] and lime[76]; in brandies[77]; and in roasted coffee.[78, 79]

[60] Schorger, "The Chemistry of Cellulose and Wood," New York, McGraw-Hill Book Co. (1926).

[61] Hawley and Wise, "The Chemistry of Wood," A. C. S. Monograph, No. 28, New York, Reinhold Publishing Corp. (1926).

[62] Günther, de Chalmot and Tollens, *Ber.*, **25**, 2569 (1892).

[63] Mann and Tollens, *Ann.*, **290**, 155 (1896).

[64] Lefevre and Tollens, *Ber.*, **40**, 4513 (1907).

[65] Fürth and Peschek, *Biochem. Z.*, **287**, 365 (1936); *C. A.*, **31**, 726 (1937).

[66] Franken, *Biochem. Z.*, **257**, 245 (1933); *C. A.*, **27**, 1881 (1933).

[67] Peter, Thaler and Täufel, *Z. Untersuch. Lebensm.*, **66**, 143 (1933); *C. A.*, **27**, 5681 (1933).

[68] Atsuki and Tomoda, *J. Soc. Chem. Ind. Japan*, **29**, 509 (1926); *C. A.*, **21**, 115 (1927).

[69] Roe, *J. Biol. Chem.*, **116**, 609 (1936).

[70] Woker and Antener, *Helv. Chim. Acta*, **20**, 732 (1937).

[71] Ono and Imoto, *J. Chem. Soc. Japan*, **59**, 1014 (1938); *C. A.*, **33**, 2128 (1939).

[72] Ikeda, Takeda, Nakama and Yokohara, *J. Chem. Soc. Japan*, **61**, 583 (1940); *C. A.*, **36**, 6754 (1942).

[73] Bohnsack, *Ber.*, **76**, 564 (1943).

[74] Hickey, *J. Org. Chem.*, **13**, 443 (1948).

[75] Bénezet, *Parfumerie*, **1**, 153 (1943); *C. A.*, **40**, 6757 (1946).

[76] Guenther and Langenau, *J. Am. Chem. Soc.*, **65**, 959 (1943).

[77] Buogo and Portincasa, *Chim. ind. agr. biol.*, **19**, 285 (1943); *C. A.*, **40**, 3223 (1946)

[78] Johnston and Frey, *J. Am. Chem. Soc.*, **60**, 1624 (1938).

[79] Hughes and Smith, *J. Soc. Chem. Ind. London*, **68**, 322 (1949).

Furfural is obtainable from vegetative materials by means other than the action of aqueous mineral acids. Steaming at about 150° will produce some furfural from pentosan-containing products. Ease of formation in some instances is reflected in the attention given to furfural and 5-(hydroxymethyl)furfural in recent publications dealing with the so-called "browning" reaction of foodstuffs. Additionally, the pyrogenetic decomposition of sugar,[51] and filter paper[80] yields small amounts of furfural, which along with furan, has also been reported in the products of the dry distillation of glucose[81] and of cotton.[82] The aldehyde is also present in the pyroligneous acid derived from both hard[51, 83] and soft[84] woods, and in wood tar and wood oil.[85, 86, 87] Data on the yield of furfural from a variety of woods under the comparatively mild conditions of pulping are reported by Aronovsky and Gortner.[88] For a more complete discussion of the occurrence of furfural in wood technology the reader is referred to texts on that general subject. It may be said, however, that the use of wood products for furfural manufacture is commercially feasible only in certain exceptional cases.

From what has gone before, it will be apparent that furfural and the chemistry of plant materials are intimately related. It is probably correct to say that almost every investigator who has done any work with vegetable products has encountered furfural at one time or another (see [89]). Stenhouse[3] called attention to this as early as 1850. Again in the 1890's, Stone[90, 91, 92] showed that agricultural wastes such as straw, corn stalks and cobs, bran, the hulls of seeds and cereals, and certain woods gave high yields of pentosans and furfural. It was in this decade that the basis was laid for the analytical determination of pentosans (p. 295). Scores of investigations were launched with the object of ascertaining the pentosan content of vegetable products, the major interest centering on the nature of the sugars, with only passing attention to the aldehyde to which these were converted. No very useful purpose would be served by giving a detailed account of this work, nor of the numerous later publications which do little more than report the potential furfural content of a host of raw

[80] Erdmann and Schaefer, *Ber.*, **43**, 2398 (1910).
[81] von Lippman, "Die Chemie der Zuckerarten," p. 301, Braunschweig (Brunswick) (1904).
[82] Sarasin, *Arch. sci. phys. et nat.*, **46**, 5 (1918).
[83] Hill, *Am. Chem. J.*, **3**, 33 (1881).
[84] Aschan, *Z. angew. Chem.*, **20**, 1811 (1907).
[85] Fischer and Laycock, *Ber.*, **22**, 101 (1889).
[86] Looft, *Ann.*, **275**, 366 (1893).
[87] Fraps, *Am. Chem. J.*, **25**, 26 (1901).
[88] Aronovsky and Gortner, *Ind. Eng. Chem.*, **22**, 264 (1930); **25**, 305, 1260 (1933).
[89] Onslow, "Principles of Plant Biochemistry," Cambridge, University Press (1931).
[90] Stone, *Am. Chem. J.*, **13**, 73 (1891).
[91] Stone, *J. Anal. Chem.*, **5**, 421 (1891); *Chem. Centr.*, **1891**, II, 892.
[92] Stone and Lotz, *Am. Chem. J.*, **19**, 348 (1897).

materials, the majority of which fail to meet the requirements of a practical source of the aldehyde. It is sufficient to point out that, to this day, the only commercial sources are plant materials which were shown many years ago to be relatively rich in pentosans.

The fact that a variety of raw materials can be processed to give furfural presents what may appear to be very intriguing possibilities to industrialists who have at hand a by-product, practically worthless except as fuel. It is interesting to note, however, that it was not until World War II, when the demand for furfural exceeded the quantity which could be made available from oat hulls,[d] that other sources (corn cobs, cottonseed hulls) were developed to the point of commercial utilization in this country.[93] Proponents of the thesis that chemicals from farm products is the road to national prosperity have frequently made extravagant claims for furfural and its relation to farm income. On the other hand, Peters[94] has pointed out that the commercial outlets for the aldehyde cannot hope to consume more than a small fraction of the available raw materials. Some of the criteria which influence the selection of a commercially suitable source material are discussed in the following paragraphs.

While theoretically all pentosan-containing substances are potentially usable, only a relatively few are technically significant. Economic considerations limit the choice to a comparatively small number which are available in large tonnages within a rather limited radius of the furfural producing plant.[93] The more important of these materials are listed in Table 1. There may be large concentrations of flax shives, sunflower seed hulls, peanut shells, etc., at certain localities which would appear to be suitable for conversion to furfural. However, an economical furfural plant requires many thousands of tons of raw material throughout the year, and this condition is rather infrequently encountered. There is a plant in Sweden which utilizes spent tan bark, and apparently the location plus the quantity of bark available has made this exception economically feasible.

It is important to recognize that, in practice, the economically recoverable yield of furfural is only 55–60 per cent of the values listed in Table 1. Accordingly, low-priced furfural is dependent upon low-priced raw material, and in estimating this cost, it is necessary to take into consideration the expense of collecting, shipping and handling the material. One of the serious drawbacks to the use of many potential sources is the cost of shipping bulky

[d] Oat hulls also have a market as a component of stock feeds wherein their value is greater than as a source of furfural. Accordingly, not all of the available hulls can be channeled into the production of furfural.

[93] Hitchcock and Duffey, *Chem. Eng. Prog.*, **44**, 669 (1948).

[94] Peters, F. N., The Quaker Oats Company, unpublished work; paper presented at Pittsburgh Meeting of the American Chemical Society, September, 1936.

products to the processing plant. This is particularly true of those substances which possess a rather high natural moisture content, and which additionally, may be only moderately rich in pentosans. Without question, freight rates, and the high capital investment in production equipment have been greater deterrents to the erection of new plant facilities than the technical difficulties involved in producing furfural. It will also be apparent that the combined properties of average moisture content, pentosan content, and bulk density of a particular raw material fix the production capacity of the plant and determine the out-turn of furfural from a digester of given capacity (p. 277). Also affecting the choice of a suitable source is the value of the by-products of the furfural process, which may vary considerably from one raw material to another. Additionally, it is obviously imperative that these by-products be readily separable from furfural in the

TABLE 1. IMPORTANT RAW MATERIALS FOR FURFURAL PRODUCTION

Raw material	Average furfural content %, dry basis, as measured by the A.O.A.C. method*
Corn cobs	23.4
Oat hulls (cleaned)	22.3
Cottonseed hull bran	21.2
Cottonseed hulls	18.6
Bagasse	17.4
Rice hulls	11.4

* See page 296.

recovery step, a requirement which presents difficulties in connection with some raw materials.

The resources for furfural production, are virtually inexhaustible. Consider only one of the raw materials listed in Table 1, namely, corn cobs. The annual corn crop in the United States corresponds to about 16 million tons of cobs, which is equivalent to almost 2 million tons of furfural, or approximately eighty times the present consumption. Of course, it is inconceivable that more than a fraction of these cobs could be made available for furfural production, but then the large tonnages of cereal and seed hulls, not to mention lower grade vegetable materials, insure adequate reserves at all times. Furfural, and its availability from annually reproducible products of the soil, affords an interesting contrast when compared with the many chemical products whose production depletes finite national resources of coal and petroleum.

FORMATION

A laboratory procedure for the preparation of furfural from plant materials, specifically corn cobs, by distillation with aqueous sulfuric acid

Table 1A. Furfural Content of Miscellaneous Plant Materials

Plant material	Furfural content %, dry basis, as measured by the A.O.A.C. method*
alfa (Morocco)	15.2
asparagus stalks	11.6
bark:	
oak	8.0
pine	6.4
barley hulls (roasted)	11.5
bean hulls	16.6
beet pulp	17.0
buckwheat hulls	16.6
castor pomace	6.6
coffee:	
bean (dark shell)	8.4
grounds	1.2
shell parchment	16.7
corn:	
bran	19.6
husks	23.9
(pop)corn cobs	23.0
cotton burrs	12.0
flax:	
chaff	7.2
shives	13.2
straw	12.8
leaves:	
cherry	8.4
elm	8.0
oak	9.8
mane vegetable (Morocco)	12.3
olive press cake	16.6
peanut:	
shells West Africa)	11.7
skins	5.1
peat moss	5.3
pecan:	
inner shells	4.6
outer shells	15.7
reed:	
cane (France)	15.6
(*arundo Donax*) (Spain)	17.9
safflower seed hulls	19.6
sorghum bagasse (Algeria)	15.9
soybean:	
bran	9.3
hulls	10.9
sudan grass	11.3
sunflower seed hulls	14.0
tung nut hulls	4.5
wheat bran	15.0
vetiver straw (Morocco)	16.0

* See p. 296. All determinations performed in The Quaker Oats Company Research Laboratories.

Table 1B. Furfural Content of Various Woods

Species	Furfural content %, dry basis, as measured by the A.O.A.C. method*
alder, red	10.9
ash:	
green	9.6
butt	10.9
middle	9.8
top	11.1
white	8.5
aspen	10.4–11.8 (13 samples)
basswood	9.7
beech, American	11.3–11.8 (2 samples)
birch:	
paper	12.4–14.0 (4 samples)
river	13.6
yellow	13.2–13.4 (2 samples)
cedar:	
incense (young growth)	7.2
southern white	5.0–5.1 (2 samples)
western red	5.2
cherry	11.7
coigue	10.0–10.1 (2 samples)
cottonwood	10.5–11.1 (2 samples)
southern	9.8
elm:	
American	9.4–10.5 (2 samples)
white	10.1
Eucalyptus, *gigantea*	7.9
fir:	
balsam	5.8–6.7 (16 samples)
Douglas	4.4–6.0 (6 samples)
noble	5.3
silver	5.4
gum, sweet	10.7–12.1 (3 samples)
hemlock:	
eastern	5.3
mountain	4.1
western	5.3 (av. of 22 samples)
larch, western	
top waste from logging	5.7
virgin stagnated old growth	5.0
maple:	
red	10.0–10.3 (2 samples)
silver	11.2
sugar	9.7
oak:	
blackjack	11.7
chestnut	11.2
overcup	10.7
post	10.4
pecan, bitter	11.2

TABLE 1B—*Continued*

Species	Furfural content %, dry basis, as measuree by the A.O.A.C. method*
pine:	
insignis (Monterey) Chilean	7.1
jack	
sapwood	7.1
heartwood	7.7
bark	4.3–4.6 (2 samples)
loblolly	
fast growth	7.3
slow growth	7.3
longleaf	
fast growth	7.2
slow growth	6.4–7.7 (2 samples)
red	5.8
shortleaf	
fast growth	7.0
slow growth	6.9–7.3 (3 samples)
slash	
fast growth	7.2
slow growth	6.4
southern	
fast growth	7.6
slow growth	6.9
white	
eastern	4.8
western	4.6–6.7 (4 samples)
poplar:	
white	13.4
yellow	10.8
spruce:	
black	6.3–7.2 (19 samples)
Engelmann	5.4–7.9 (3 samples)
Sitka	4.3
white	6.9–7.2 (2 samples)
sugarberry	12.6
tamarack	4.8 (2 samples)
Tamarix	10.4
tepa	8.0–10.3 (2 samples)
tupelo:	
black (swamp)	10.0
water	10.0
gum	9.0
ulmo	8.7
willow, black	10.9

* See page 296. All values calculated from values for pentosan content reported by Forest Products Laboratory[94a] using the appropriate factor derived from Kröber's tables.

has been described by Adams.[95, 96] The conversion involves two major reactions which may be designated as (a) hydrolysis of pentosans and (b) transformation of pentose into furfural. While these reactions proceed simultaneously in the single-stage manufacturing process (p. 277), the first takes place much more rapidly than the second, and they can be studied separately.

Hydrolysis of Pentosans

By comparison with the wealth of information available on the saccharification of cellulose and wood,[97, 98] data concerning the acid hydrolysis of hemicelluloses, particularly pentosans, are quite meager. However, it has been demonstrated with wood,[99, 100] and with agricultural residues,[101] that it is possible to carry out a partial hydrolysis with dilute acid at relatively low temperature to obtain pentose liquors (and/or furfural) without significantly degrading the cellulose. The latter is, of course, subject to saccharification under more strenuous conditions, and several industrial processes involving such step-wise hydrolysis of vegetative materials have been worked out for the production of low pentosan pulps, or fermentable sugars, with pentose or furfural as by-products (p. 277).

According to Dunning and Lathrop[101] separation of the pentosans (as pentose plus furfural) in corn cobs can be effected in 95 per cent yield with only limited attack on the lignocellulosic component. However, Wilson[102] was unable to duplicate this result, obtaining at best 83–84 per cent under similar conditions of temperature, time, acid strength and liquid/solid ratio. The discrepancy is traceable to the different analytical procedures employed. Reproducibility of results is obviously dependent upon estimation of the pentosan content of the charge material (p. 296). On the other hand, the term "pentosan" does not refer to a uniform material, hence the problem assumes a complexity which is, perhaps, not immediately apparent. In related studies,[103] the difficulty has been at least partially avoided by estimating all the furfural precursors together as potential

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[94a] Forests Products Laboratory, "Physical and Chemical Properties of Various Pulping Hardwoods and Softwoods Received at Forest Products Laboratory from July, 1935 to October 1, 1948," Reports M 85183F, M 85184F and M 85185F, U. S. Dept. Agriculture, Forest Service, Madison, Wis.

[95] Adams and Voorhees, "Organic Syntheses," Collective Vol. 1, p. 274, New York, John Wiley and Sons (1932).

[96] Adams, Kamm and Marvel, University of Illinois, Bulletin 16, No. 43 (1919).

[97] Saeman, *Ind. Eng. Chem.*, **37**, 43 (1945).

[98] Whipple, *Rept. Vermont Wood Products Conf.*, **5**, 13 (1945); *C. A.*, **40**, 2623 (1946).

[99] Katzen and Othmer, *Ind. Eng. Chem.*, **34**, 314 (1942).

[100] Katzen, Aries and Othmer, *Ind. Eng. Chem.*, **37**, 442 (1945).

[101] Dunning and Lathrop *Ind. Eng. Chem.*, **37**, 24 (1945).

[102] Wilson, *J. Council Sci. Ind. Research*, **20**, 258 (1947).

[103] The Quaker Oats Company, unpublished work.

furfural. In this way it is possible to follow the hydrolysis of the precursors to water-soluble form. Under mild conditions such that comparatively little furfural is formed, an excellent material balance can be obtained. Thus, in Table 2, data are presented concerning the acid-hydrolysis of the furfural-forming constituents of corn cobs. Ground cobs were charged to a flask fitted with a reflux condenser. Dilute sulfuric acid, preheated to 90°, was added to give the desired liquid/solid ratio, following which the temperature was raised rapidly to 100°, and maintained for the indicated period of time. At this point the mixture was chilled, filtered, and the residue washed thoroughly with water to complete the removal of soluble

TABLE 2. ACID HYDROLYSIS OF FURFURAL PRECURSORS IN CORN COBS[103]

Temperature	100°
Concn. of H_2SO_4	0.916 *N*
Solid/liquid ratio	1/18

Material balance*	Reaction time (min.)				
	30	60	128	300	420
Hydrolyzate:					
potential furfural (as furfural)	73.0	75.3	80.9	84.6	83.6
free furfural	2.0	2.4	2.5	4.1	6.7
Residual cobs:					
potential furfural (as furfural)	23.7	22.6	16.3	11.2	7.9
Total accounted for	98.7	100.3	99.7	99.9	98.2

* All values expressed as percentage of the potential furfural charged. The latter value was obtained by A.O.A.C. distillation of the cobs (p. 296), estimation of the furfural so produced using the bromine method of Hughes and Acree (pp. 296, 299), and accepting this value as 89% of the actual potential (p. 304).

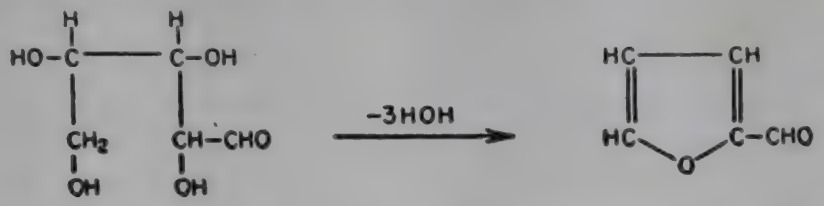
precursors and any furfural which might have been formed. The combined filtrate and washings are designated as hydrolyzate, the remaining solid material as residual cobs. There was very little destruction of precursor or furfural during the course of the experiment, although under other experimental conditions such losses can be significant.[102] In confirmation of the observation of Wilson[102] (see also [104]) it is apparent that about 75 per cent of the precursors are readily hydrolyzable, the remainder much more difficultly so. Thus, in the experiment under discussion, the average rate of conversion to water-soluble form was approximately 0.048/min.[e] during the first thirty minutes. This rate fell off rapidly; the average value during

[e] At the liquid/solid ratio employed, the change in concentration of water may be considered to be insignificant, and the hydrolysis reaction can be expected to follow the equation of a first order reaction (pseudo-unimolecular). The rate values were

the following half-hour period was 0.005/min., which progressively decreased to 0.002/min. and remained more or less constant over the period of the last three hours. Other raw materials which were tested (oat hulls, cottonseed hulls and rice hulls) behaved similarly.[103]

Conversion of Pentose to Furfural

The formation of furfural from aldopentoses[f] may be schematically illustrated as the elimination of three moles of water:



However, the reaction is not a simple dehydration, since dehydrating catalysts (zinc chloride, phosphorus pentoxide, etc.) produce negligible yields of furfural from xylose.[105] Additionally, while xylose loses water by the action of heat alone, the major product is xylosan,[g] not furfural.[106]

The mechanism of the furfural-forming reaction has not been unequivocally established. In 1932, Hurd[105] proposed a scheme involving formation of the conjugated enol, II, as the key intermediate, and support for this hypothesis is seen in the spectroscopic evidence obtained recently by Wolfrom.[107] Hurd reasoned that, as a β-hydroxy carbonyl compound, the open-chain aldehyde form (I) of xylose is subject to facile dehydration in the well-established manner of such types to give II; that II undergoes cyclodehydration to III from which furfural is derived following the elimination of another mole of water. The fact that *meso*-erythritol failed to produce furan under the same experimental conditions led Hurd to the conclusion that the presence of a β-hydroxy aldehyde, I, is a necessary condition for the reaction, and that formation of the heterocyclic ring is preceded by dehydration of I to the α,β-unsaturated aldehyde, II. Wolfrom[107] is in substantial agreement with this viewpoint, but suggests an alternative

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calculated on this basis, the percentage hydrolysis for a given time interval being estimated from a plot of the extent of hydrolysis (difference between 100 and the value for potential furfural in residue, see Table 2) versus the duration of reaction.

[f] Distillation of a polymeric form of ketoxylose, $CH_2OH(CHOH)_2COCH_2OH$, with 7.5*N* sulfuric acid produced furfural in approximately 5 per cent yield.[105]

[g] Xylosan gave rise to 75 per cent of the theoretical amount of furfural on distillation with 12 per cent hydrochloric acid over a period of 24 hours. The slow rate of conversion was attributed to the resistance of the xylosan to hydrolysis.[106]

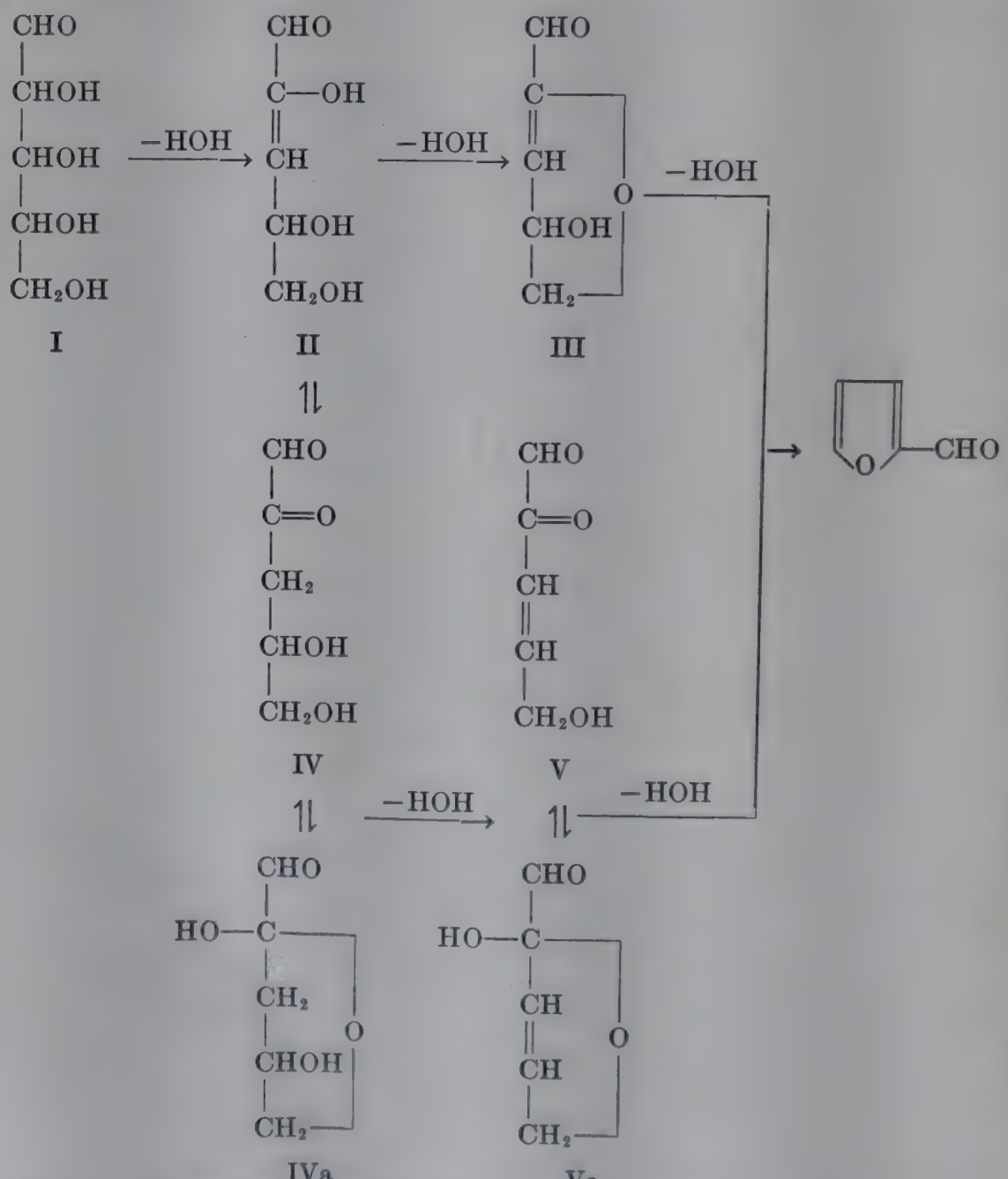
[104] Sorgato, *Ricerche sez. sper. zuccheri, R. univ. stud. Padova, Ist. chim. ind.*, **4**, 35 (1949); *C. A.*, **44**, 6822 (1950).

[105] Hurd and Isenhour, *J. Am. Chem. Soc.*, **54**, 317 (1932).

[106] Hurd and Isenhour, *J. Am. Chem. Soc.*, **54**, 693 (1932).

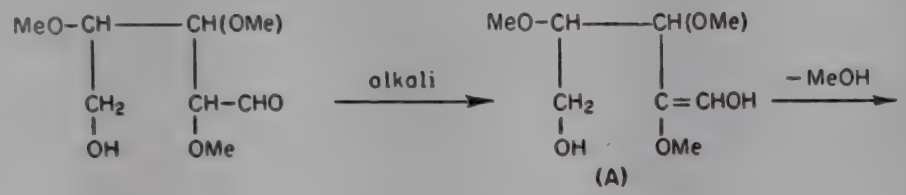
[107] (a) Wolfrom, Schuetz and Cavalieri, *J. Am. Chem. Soc.*, **70**, 514 (1948); (b) *Ibid.*, **71**, 3518 (1949).

route from II to furfural. He proposes that II, in the form of its keto tautomer, IV, loses water from its β-hydroxy carbonyl system to produce V, which upon final dehydration gives rise to furfural. In support of this postulate he refers to the isolation of an analog of V (in the form of its phenylosazone) by the action of hydrochloric acid on tetramethylglucoseen.[108] Intermediates IV and V can be in equilibrium with their cyclic hemiacetal forms, IVa and Va. An electronic interpretation of the course of reaction involving the same intermediates has been put forward by Isbell.[109] However, it should be borne in mind that none of the intermediate products has been isolated as such, and that a final solution to this challenging problem is still pending.

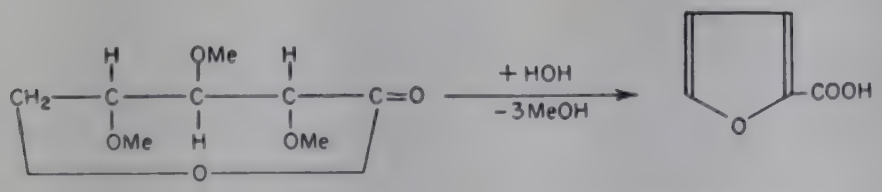


[108] Wolfrom, Wallace and Metcalf, *J. Am. Chem. Soc.*, **64**, 265 (1942).
[109] Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944).

Furfural has been obtained from methylated derivatives of xylose and arabinose.[h] Carruthers and Hirst[111] report its formation from methyl trimethylxyloside by the action of hydrochloric acid, and Lewis has shown that alkali-equilibrated trimethylxylose[112] and trimethylarabinose[113] similarly give rise to furfural under the influence of small amounts of acid. Lewis proposed a mechanism for the reaction involving the formation of an intermediate enolic modification, A,[i] which readily loses methyl alcohol, following which the de-enolizing action of acid is accompanied by further elimination of the alcohol and formation of furfural. For the convenience of the reader, these steps are presented below, although it is believed that the transformation is better interpreted in terms of an enol intermediate analogous to that (see II, above) proposed by Hurd for the conversion of free xylose (see [109]).



[h] Related to this is the transformation of 2,3,4-trimethylxylonolactone into 2-furoic acid when heated in aqueous pyridine.[110]



[i] A similar intermediate has been proposed to account for the formation of 5-(hydroxymethyl)furfural from glucose, and from the fructose portion of the sucrose molecule.[114] However, for the direct conversion of glucose, Wolfrom[107a] presents spectroscopic evidence in favor of a conjugated enol intermediate analogous to II shown above (see p. 409).

[110] Haworth and Long, *J. Chem. Soc.*, **1929**, 345.

[111] Carruthers and Hirst. *J. Chem. Soc.*, **121**, 2299 (1922).

[112] Gross and Lewis, *J. Am. Chem. Soc.*, **53**, 2772 (1931).

[113] Neher and Lewis, *J. Am. Chem. Soc.*, **53**, 4411 (1931).

[114] Haworth and Jones, *J. Chem. Soc.*, **1944**, 667.

The relative ease of conversion of methylated pentoses of both furanose and pyranose configuration was investigated by Bott and Hirst.[115] The rates of reaction of these types, and of unsubstituted xylose and arabinose are listed in Table 3, which also includes the maximum obtainable yield of furfural under the conditions employed. Like the parent sugars, the methylated derivatives of arabinose exhibit a slower rate of reaction than the corresponding derivatives of xylose.[j]

In most instances, the yield of furfural is by no means quantitative, hence kinetic studies have necessarily been concerned primarily with the rate of disappearance of pentose rather than with the rate of formation of the aldehyde. The rate of disappearance of xylose in aqueous, acidic medium has been shown[105, 106, 97, 102, 117] (see also [118]) to follow the equation of a

Table 3. Conversion of Methylated Pentoses to Furfural[115]

Sugar	Time for 50% conversion* (hrs.)	Maximum yield of furfural (%)
Xylose	1.6	92
Trimethylxylofuranose	2.4	34
Trimethylxylopyranose	1.2	80
Arabinose	2.8	76
Trimethylarabofuranose	3.4	93
Trimethylarabopyranose	12.0	66

* Conditions of conversion similar to those employed in the A.O.A.C. distillation using 12% aqueous hydrochloric acid (p. 296).

first order reaction, $-\frac{dC}{dt} = kC$. Over the range of temperatures observed (100–210°), and at a hydrogen ion concentration of 0.05 equivalents per liter, the reaction rate, k, can be expressed in terms of the Arrhenius equation as shown below[103]:

$$\log k = -\frac{7000}{T} + 14.17$$

where k is in min.$^{-1}$, and T is the absolute temperature. Since the rate, k, is directly proportional to the hydrogen ion concentration over a relatively

[j] It is interesting to note the increased stability toward acids shown by tetramethylglucopyranose. This product, which differs from trimethylxylopyranose only in the terminal group, is almost unaffected by boiling 8 per cent hydrochloric acid.[115] See, however, the transformation of tetramethylfructofuranose[116] and tetramethylglucoseen[108] into 5-(methoxymethyl)furfural by the action of hydrochloric acid.

[115] Bott and Hirst, *J. Chem. Soc.*, **1932**, 2621.

[116] Haworth, Hirst and Nicholson, *J. Chem. Soc.*, **1927**, 1513.

[117] Dunlop, *Ind. Eng. Chem.*, **40**, 204 (1948).

[118] Cooke, *Paper Trade J.*, **117**, 32 (1943).

wide range,[103] a more general expression may be written:

$$k = \left(\frac{[H^+]}{0.05}\right) 10^{(-7000/T+14.17)}$$

where $[H^+]$ is in equiv./liter.

Similarly, the conversion of arabinose to furfural, as measured by the rate of disappearance of the sugar, gives first order reaction constants, but the rate is only 55–60 per cent of that observed with xylose[97, 119, 115, 120] (see also [121]). Thus, the stereochemical configuration of the pentose molecule exerts considerable influence upon the formation of furfural. Arabinose is more stable toward aqueous acid than is xylose, and as shown earlier (Table 3), this effect is carried over to the methylated derivatives of these sugars. Hurd[105] believes that there may be a relationship between the relative ease of formation of furfural and the velocity of mutarotation of the pentoses (see also [122]).

Conflicting reports appear in the literature relating to the yield of furfural obtainable from pentoses. Much work has been carried out to ascertain the relative merits of a variety of acid catalysts and acid-salt mixtures. In their review of the early work, Pervier and Gortner[123, 124] refer to the use of hydrochloric, sulfuric, phosphoric and glacial acetic acids. Hurd and Isenhour[105] (see also [125]) demonstrated that nitric, oxalic and trichloroacetic acids were relatively ineffective under the conditions employed; that of the acids tested, only sulfuric acid (see also [126, 127]) and preferably hydrochloric acid (see also [128, 91, 129]) were productive of good yields of furfural from xylose when distilled with the acid at atmospheric pressure (*ca.* 100°). At yet higher temperatures, weaker acids may be employed, and of course, furfural can be obtained in the absence of a catalyst by simply heating an aqueous solution of xylose. Contrary to the findings of Jayme and Sarten,[130] Adams and Castagne[131] have demonstrated that hydrobromic acid has no advantage over hydrochloric acid.

[119] Kremann and Klein, *Monatsh.*, **38**, 63 (1917); *C. A.*, **11**, 2988 (1917).
[120] Hughes and Acree, *J. Research Natl. Bur. Standards*, **23**, 293 (1939).
[121] Ashmarin and Vasil'kova, *Bull. biol. med. exptl. U.R.S.S.*, **4**, 363 (1937); *C. A.*, **34**, 4971 (1940).
[122] Singh, Dean and Cantor, *J. Am. Chem. Soc.*, **70**, 517 (1948).
[123] Pervier and Gortner, *Ind. Eng. Chem.*, **15**, 1167 (1923).
[124] Pervier and Gortner, *Ind. Eng. Chem.*, **15**, 1255 (1923).
[125] Andrews and Milroy, *Biochem. J.*, **27**, 1421 (1933).
[126] Cross, Bevan and Smith, *Ber.*, **28**, 1940 (1895).
[127] Menaul and Dowell, *Ind. Eng. Chem.*, **11**, 1024 (1919).
[128] Allen and Tollens, *Ber.*, **23**, 137 (1890).
[129] Ling and Nanji, *Biochem. J.*, **15**, 466 (1921).
[130] Jayme and Sarten, *Naturwissenschaften*, **28**, 822 (1940); *C. A.*, **35**, 5065 (1941); *Biochem. Z.*, **308**, 109 (1941); *C. A.*, **37**, 1348 (1943).
[131] Adams and Castagne, *Can. J. Research*, **B26**, 309 (1948).

In analytical work, 12 per cent hydrochloric acid is the reagent most commonly employed. Under the conditions of the A.O.A.C. (p. 296) distillation procedure (the distillate is collected at a rate of 3 cc. per minute over a period of two hours), this reagent gives a recovery of 88–90 per cent of the theoretical amount of furfural from xylose, and approximately 75 per cent from arabinose[120] when operating within the specified limits of concentration of these sugars. For obvious reasons, considerable effort has has been expended in the development of procedures which will effect quantitative conversion (see references p. 296); procedures, for the most part, tedious and of uncertain reproducibility.[132] Pervier and Gortner[123, 124] reasoned that the loss in yield was due to destruction of furfural in the acid medium in which it is formed. Accordingly, they recommended rapid steam distillation (see also [133, 134, 135]) during the conversion in order to remove the furfural more rapidly from the reaction zone. Related to this is the use of acid-salt mixtures as conversion media, with the idea of salting-out the aldehyde and thereby assisting in its rapid removal.[136, 137, 138] In the hands of Hughes and Acree, the combination of steaming and salting-out, using 12 per cent hydrochloric acid saturated with sodium chloride, produced quantitative yields of furfural from xylose[139] (compare Launer and Wilson[140]) and arabinose,[120] and of 5-methylfurfural from rhamnose.[120] Among other things, the inclusion of salt accelerates the rate of furfural formation,[131] probably by a combination of effects, (1) elevation of the reflux temperature of the medium and (2) increase of the activity coefficient of the acid.[138] Yet another scheme which has been employed in an attempt to minimize destruction of furfural by the acidic medium is to carry out the pentose conversion in the presence of a water-insoluble solvent such as toluene.[141, 138, 142] However, while the yield of furfural is dependent upon its rapid removal,[k] it can be shown that destruction of the aldehyde by acid

[k] The yield varies with the rate of distillation, which regulates the concentration of free furfural in the medium. At a fixed distillation rate, the latter is, of course, a function of the pentose concentration, hence yield is also influenced by the amount of available pentose.[103] These facts emphasize the necessity for strict adherence to prescribed experimental conditions if one is to obtain reproducible results whether by use of the A.O.A.C. analytical procedure (p. 296) or the many modifications which have been proposed.

[132] Jayme and Sarten, *Biochem. Z.*, **310**, 1 (1941); *C. A.*, **37**, 3021 (1943).

[133] Jolles, *Sitzb. Akad. Wiss. Wien*, **IIb**, 114, 1191 (1905).

[134] Youngburg, *J. Biol. Chem.*, **73**, 599 (1927).

[135] Bailey, *Mikrochim. Acta*, **2**, 35 (1937); *C. A.*, **32**, 458 (1938).

[136] Kullgren and Tyden, *Ing. Vetenskaps Akad. Handl.*, **94**, 3 (1929); *C. A.*, **24**, 1316 (1930).

[137] Kline and Acree, *J. Research Natl. Bur. Standards*, **8**, 25 (1932).

[138] Fulmer, Christensen, Hixon and Foster, *J. Phys. Chem.*, **40**, 133 (1936).

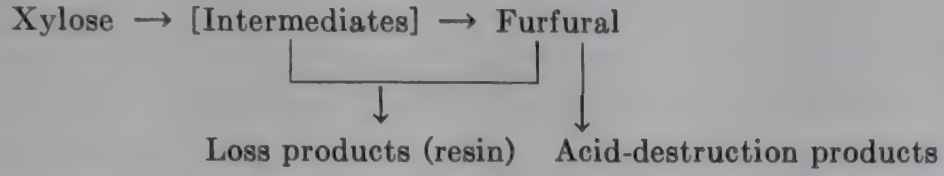
[139] Hughes and Acree, *J. Research Natl. Bur. Standards*, **21**, 327 (1938).

[140] Launer and Wilson, *J. Research Natl. Bur. Standards*, **22**, 471 (1939).

[141] Foster, *Iowa State Coll. J. Sci.*, **8**, 191 (1933).

[142] Reeves and Munro, *Ind. Eng. Chem., Anal. Ed.*, **12**, 551 (1940).

is not the major source of loss in the ordinary A.O.A.C. acid-distillation of xylose; that failure to attain quantitative yields is due principally to the reaction of furfural with an intermediate product(s) generated in the conversion step.



Results obtained in this laboratory as well as those reported by others[136, 137, 131] demonstrate that furfural is recoverable in high yield (97–99 per cent) on distillation from strong, aqueous acid solution. (For the kinetics of destruction of furfural in aqueous, acidic medium, see [143].) Accordingly, acid-destruction of the aldehyde fails to account for more than a fraction of the loss under discussion. Neither can this loss be attributed to side reactions whereby xylose, or the intermediate products, are decomposed to compounds other than furfural, since it is possible to obtain quantitative yields from xylose[103, 139] by providing for more or less instantaneous removal of the aldehyde as it is formed. These facts suggest that the underlying cause of low yields is a secondary reaction(s) between furfural and an intermediate, or between furfural and xylose itself. However, it has been established[103] that, under controlled conditions of partial conversion, the amount of free furfural in the reaction medium has no effect on the quantity of unchanged xylose. Therefore, it may be concluded that the principal source of loss in yield is the reaction of furfural with one or more intermediates[117] as illustrated in the above diagram (see also [104]).

Analytical Methods

While most of the material to be dealt with here is concerned with analytical procedures for furfural itself, adequate treatment demands some reference to the determination of pentoses and pentosans. On the other hand, there seems little necessity to discuss numerous publications which are concerned solely or primarily with these carbohydrates. For a review and critique of some of the literature on this subject to 1923, the interested reader is referred to the excellent papers of Pervier and Gortner.[123, 124] In this monograph, discussion of the pentosan–furfural relationship is confined essentially to the standard analytical method for pentosans, and to a consideration of this method in terms of the potential furfural content of plant materials.

Estimation of Pentosans and Potential Furfural in Vegetable Products

As intimated previously (p. 287), pentosans are not measured directly. None of the analytical methods is entirely satisfactory, but that adopted

[143] Williams and Dunlop, *Ind. Eng. Chem.*, **40**, 239 (1948).

by the Association of Official Agricultural Chemists[144a] (see also [145]) is more widely used than any other (see also [146, 147, 148]). This procedure involves conversion of the pentoses or pentosans into furfural by distillation of the source material with 12 per cent hydrochloric acid under carefully specified conditions. The furfural in the distillate is then precipitated with phloroglucinol, and the weight of phloroglucide is calculated in terms of pentose or pentosan in accordance with certain empirical relationships derived by Kröber.

The method has several inherent inaccuracies, and has been the subject of many investigations. Some of the factors involved are indicated below:

(1) Pentoses do not yield the theoretical quantity of furfural under the distillation conditions employed. Xylose gives approximately 89 per cent of the calculated amount, arabinose about 75 per cent. This has been attributed by some investigators to partial resinification of furfural by the acid. However, destruction in this manner fails to account for more than a fraction[137] of the loss, which is due primarily to condensation of furfural with some intermediate product(s) (see p. 295). Many modified distillation procedures have been proposed in order to attain quantitative conversion, and for xylose this can be accomplished by passing steam at a very high rate through the reaction mixture during the acid digestion.[103] As expected, the required steam flow rate varies directly with the concentration of xylose. This procedure is unwieldly and ill-adapted to analytical work, however, and the A.O.A.C. distillation technique remains unchanged to date. Literature dealing with this general topic includes Pervier and Gortner,[124] Hoffman,[149] Youngburg,[134] Kullgren and Tyden,[136] Suminokura,[150] Iddles and Robbins,[151] Bailey,[135] Hughes and Acree,[139] Hallsworth,[152] Reeves and Munro,[142] Jayme and Sarten,[130] Vernon and Metzner,[153] Duncan,[154] Duffau,[155] Adams and Castagne.[131]

(2) Components of plant materials other than pentoses and pentosans can produce furfural under the conditions of acid-distillation (see p. 279). Consequently, the determination of furfural, even if this were produced

[144] (a) "Official and Tentative Methods of Analysis," 4th Ed., p. 344, Washington, Association of Official Agricultural Chemists, 1935; (b) *Ibid.*, p. 171.

[145] Kröber, *J. Landw.*, **48**, 357 (1900); **49**, 7 (1901); *Chem. Centr.*, **1901**, I, 477, 1119.

[146] Gierisch, *Cellulosechemie*, **6**, 61 (1925); *C. A.*, **19**, 3072 (1925).

[147] Takehara, *J. Soc. Chem. Ind. Japan*, **46**, 449, 452 (1943); **47**, 71, 423, 425, 553 (1944); *C. A.*, **43**, 1975–1977 (1949).

[148] Teunissen, *Anal. Chem.*, **21**, 620 (1949).

[149] Hoffman, *J. Biol. Chem.*, **73**, 15 (1927).

[150] Suminokura, *J. Biochem. Japan*, **14**, 343 (1931); *C. A.*, **26**, 1216 (1932).

[151] Iddles and Robbins. *Ind. Eng. Chem., Anal. Ed.*, **5**, 55 (1933).

[152] Hallsworth, *J. Soc. Chem. Ind.*, **58**, 357 (1939).

[153] Vernon and Metzner, *Cereal Chem.*, **18**, 572 (1941).

[154] Duncan, *Ind. Eng. Chem., Anal. Ed.*, **15**, 162 (1943).

[155] Duffau, *Bull. soc. chim. biol.*, **28**, 873 (1946); *C. A.*, **41**, 3016 (1947).

quantitatively, is not a completely accurate basis for calculation of the "pentosan" content of such materials.

(3) Precipitation of furfural with phloroglucinol is not quantitative and the relationship of the phloroglucide to any one of the precursors of furfural is strictly empirical, including among other factors, a correction for the solubility of the precipitate. As set up by Kröber, the relationship is merely an approximation, and is valid over a narrower range than he proposed.[156]

(4) The composition of the phloroglucide obtained from furfural and phloroglucinol may be variable.[157, 158, 159, 160, 145, 161, 162, 163, 164, 165] Additionally, the phloroglucide precipitate may include derivatives of aldehydes other than furfural, such as 5-methylfurfural and 5-(hydroxymethyl)furfural derived, respectively, from methylpentoses and hexoses from the original plant material.[166, 167, 168, 169, 170, 171, 172, 146, 136, 173, 67, 174, 153]

It is quite apparent that this, the official method, leaves much to be desired[140, 175, 118] even if one had at hand a completely accurate method for measuring furfural which was not subject to interference by other substances. Obviously, values for the pentosan content of plant materials must be accepted with reservation, since it is not possible to relate furfural to any specific precursor without prior knowledge of which precursors are present, and in what ratio. In the interest of accuracy, it would appear that the method should be revised, or completely discarded, although this would probably cause a great deal of confusion in connection with the

[156] Angell, Norris and Resch, *Biochem. J.*, **30**, 2146 (1936).
[157] Votoček, *Ber.*, **30**, 1195 (1897).
[158] Hotter, *Chem. Ztg.*, **17**, 1743 (1893); *Chem. Centr.*, **1894**, I, 115.
[159] Councler, *Chem. Ztg.*, **18**, 966 (1894); *Chem. Centr.*, **1894**, II, 221.
[160] Welbel and Zeisel, *Monatsh.*, **16**, 283 (1895); *Chem. Centr.*, **1895**, II, 33.
[161] Goodwin and Tollens, *Ber.*, **37**, 315 (1904).
[162] Wenzel and Lazar, *Monatsh.*, **34**, 1913 (1913); *C. A.*, **8**, 502 (1914).
[163] Votoček and Potmesil, *Ber.*, **49**, 1185 (1916).
[164] Votoček and Krauz, *Z. Zuckerind. Böhmen*, **34**, 20 (1910); *C. A.*, **4**, 127 (1910).
[165] Trost, *Boll. soc. adriatica sci. naturali Trieste*, **31**, 5 (1932); *C. A.*, **29**, 7324 (1935).
[166] Fraps, *Am. Chem. J.*, **25**, 501 (1901).
[167] Cunningham and Dorée, *Biochem. J.*, **8**, 438 (1914).
[168] Testoni, *Staz. sper. agrar. ital.*, **50**, 97 (1917); *Chem. Centr.*, **1918**, II, 865.
[169] Tadokoro, *J. Coll. Agr. Hokkaido Imp. Univ.*, **10**, 37, 50 (1921); *C. A.*, **16**, 1183 (1922).
[170] Heuser and Stöckigt, *Cellulosechemie*, **3**, 61 (1922); *C. A.*, **16**, 2988 (1922); Heuser and Eisenring, *Ibid.*, **4**, 13, 25 (1923); *C. A.*, **17**, 3249 (1923); Heuser and Schott, *Ibid.*, **4**, 85 (1923); *C. A.*, **18**, 391 (1924); Heuser and Dammel, *Ibid.*, **5**, 45 (1924); *C. A.*, **18**, 2806 (1924).
[171] Report of the Committee of the Division of Cellulose Chemistry of the American Chemical Society, *Ind. Eng. Chem.*, **15**, 748 (1923).
[172] Klingstedt, *Z. anal. Chem.*, **66**, 129 (1925); *C. A.*, **19**, 2465 (1925).
[173] Schmidt-Nielsen and Hammer, *Kgl. Norske Videnskab. Selskab. Forh.*, **5**, 84 (1932); *C. A.*, **27**, 1296 (1933).
[174] Marshall and Norris, *Biochem. J.*, **31**, 1939 (1937).
[175] Hockett, Guttag and Smith, *J. Am. Chem. Soc.*, **65**, 1(1943).

tremendous amount of published work wherein furfural figures have been used for the calculation of pentose or pentosan.

In this book of course, our chief concern is with the "potential furfural" content rather than the "pentosan" content of vegetable products. To a certain extent, this simplifies the interpretation of analytical results, but even here, considerable uncertainty remains. Thus, for a given weight of phloroglucide precipitate, one may arrive at a value for furfural by use of Kröber's empirical equation[1] (see p. 297):

$$F = (P + 0.0052) \times 0.5185$$

where F = furfural; P = phloroglucide in the range 0.03 to 0.30 gram. By this procedure, if the phloroglucide precipitate includes, in addition to furfural phloroglucide, the corresponding derivatives of other[m] volatile aldehydes, the calculated value for furfural will be somewhat higher[n] than the actual amount. Again, when reporting the result in terms of potential furfural content of a particular raw material there is introduced a yet greater error in the other direction, due to the fact that the furfural-precursors are not quantitatively converted to the aldehyde.

It may be fairly concluded that it is not possible, at this time, to ascertain the "potential furfural content" of a plant material, although this term has been used, or implied, in many published papers. As a compromise, we have

[1] Angell[156] offers the following modified equation as one which more precisely expresses the absolute relationship between furfural and the phloroglucide.

$$F = 0.5030P + 0.0018 \pm 0.0003 \text{ (for P in the range 0.053 to 0.123).}$$

Of course, proper use of either equation demands strict adherence to carefully defined conditions. Kröber's equation may be applied only to analytical data derived in accordance with the A.O.A.C. procedure. Angell's precipitation technique involves some modification of the latter, therefore the use of his equation must be restricted to results obtained by his procedure.

[m] Kullgren and Tyden[136] (see also [176]) report that redistillation of the original distillate, prior to precipitation with phloroglucinol, decomposes any 5-(hydroxymethyl)furfural which may be present, destroys about one-third of any 5-methylfurfural and about 3 per cent of the furfural. Other schemes have been proposed for eliminating these interfering aldehydes, including several which depend upon the differential solubilities of the mixed phloroglucides (see [166, 167, 168, 169, 170, 171, 172, 146, 136, 173, 67, 174, 153]). None of these procedures has received universal acceptance.

[n] Methylfurfural-forming substances, methylpentosans, are relatively scarce in nature, hence in most analyses the presence of this aldehyde can be more or less disregarded. (Hydroxymethyl)furfural, derived from hexosans and cellulose, is largely destroyed under the conditions of acid-distillation, and here too, only a small error is likely to be introduced. Some indication of the magnitude is seen in the work of Adams and Castagne.[131] However, their results are not directly applicable to the method under discussion since (1) they employed a modified distillation technique which would be expected to increase the (hydroxymethyl)furfural content of the distillate, and (2) they determined the furfural yield by means other than precipitation with phloroglucinol.

[176] Mackney and Reynolds, *J. Council Sci. Ind. Research*, **11**, 333 (1938).

resorted to reporting results as "furfural-measured by the A.O.A.C. procedure," and the values listed in Table 1 were so derived. It is recognized that these values are considerably lower than the "potential furfural content"; about 89 per cent[o] of the latter, if we assume that the furfural is largely derived from xylose, an assumption which is probably valid for most of the raw materials with which we are concerned. The second step of the analysis, measurement of furfural by precipitation with phloroglucinol, is time-consuming and of questionable accuracy in a single determination (p. 297). Accordingly, analysts in The Quaker Oats Company laboratory prefer to use the bromate-bromide procedure of Hughes and Acree (p. 304), although it should be observed that the average results of a great many determinations using both methods are very nearly identical.

Estimation of Furfural

In the present state of our knowledge, the quantitative estimation of furfural presents a number of difficulties, not the least of which is selection of a satisfactory method in any particular instance. Of the multiplicity of analytical procedures which have been proposed, none has received universal acceptance. For the most part, they can be divided into two general categories, (1) those involving reactions of the aldehyde group, and (2) those which are dependent upon behavior characteristics of the furan ring. Accordingly, the determination of furfural is generally subject to interference by carbonyl compounds or other unsaturated substances. There is also the difficulty that, even when analyzing for furfural in the absence of interfering contaminants, most of the methods leave much to be desired from the standpoint of accuracy and reproducibility. Thus, no procedure yet described is completely suitable for assaying the furfural content (approx. 99.5 per cent) of commercial furfural. For specification purposes, this can only be accomplished by measuring the known impurities.

To a certain extent, choice of a method depends upon the purpose at hand. Thus, if the determination of furfural is for calculation of pentosan, as in feed analyses, expediency more or less demands use of the phloroglucinol procedure. For a quick estimation of furfural where relative amounts may be as important as absolute values, a colorimetric procedure, or possibly a bisulfite-iodine method is to be preferred. As a result of long experience, we recommend the bromine methods of Hughes and Acree[177]

[o] One mole of xylose (M.W. = 150) can theoretically produce one mole of furfural (M.W. = 96). Thus, the theoretical yield of the aldehyde is 64 per cent of the available xylose. However, a check of Kröber's tables reveals that for a given amount of xylose, the corresponding value for furfural is only 57 per cent of this amount. This is because the A.O.A.C. distillation procedure produces only 89 per cent of the theoretical quantity of furfural from xylose.

[177] Hughes and Acree, *Ind. Eng. Chem., Anal. Ed.*, **6**, 123 (1934).

or Kullgren and Tyden[136] as the most generally satisfactory analytical procedures where the problem calls for the greatest possible accuracy. The former has been adopted as the standard procedure in the laboratories of The Quaker Oats Company.

In the following paragraphs, the better known analytical methods are discussed, including the results of several years of intensive study of the subject by Howells.[178] For further information dealing with the comparison of various methods, reference to the following papers is recommended: Tollens,[179] Kline and Acree,[137] Schmidt-Neilson and Hammer,[173] Iddles and Robbins,[151] Sadikov and Belikova,[180] Krishnan,[181] Volodutzkaya and Khovanskaya,[182] Campbell and Smith,[183] Mackney and Reynolds.[176]

Gravimetric Methods:

Determination with Phloroglucinol. Phloroglucinol was first used as a colorimetric reagent for furfural by Wheeler and Tollens in 1889.[184] Later, Hotter[158] showed that the isomeric pyrogallol would precipitate furfural from aqueous solution, and this led Councler[159] to try phloroglucinol for the same purpose. The procedure employed in the second step of the A.O.A.C. analytical method for pentosans (p. 296) is essentially Kröber's modification of Councler's method, but for those interested in the historical development, reference to the following is recommended: Kruger and Tollens,[185] Komers and Stift,[186] Grégoire and Carpiaux,[187] Kröber,[145] Kröber and Rimbach,[188] Tollens,[179] Ellet and Tollens.[189]

The shortcomings of the method as applied to the measurement of furfural obtained from plant materials were mentioned on p. 296. It will be apparent that some of these criticisms are pertinent also when the method is used for analysis of solutions of pure furfural. Little additional

[178] Howells, H. P., The Quaker Oats Company, paper presented at Pittsburgh Meeting of the American Chemical Society, September, 1936.

[179] Tollens, *Z. physiol. Chem.*, **36**, 329 (1902); *Ber.*, **36**, 261 (1903).

[180] Sadikov and Belikova, *Schriften zentral. biochem. Forsch.-Inst. Nahr.-Genussmittelind. U.S.S.R.*, **3**, 299 (1933); *C. A.*, **28**, 3029 (1934).

[181] Krishnan, *J. Indian Chem. Soc.*, **11**, 651 (1934); *C. A.*, **29**, 708 (1935).

[182] Volodutzkaya and Khovanskaya, *Trudui VNIIZh* **1934**, No. 2, 101; *C. A.*, **29**, 7870 (1935).

[183] Campbell and Smith, *Biochem. J.*, **31**, 535 (1937).

[184] Wheeler and Tollens, *Ann.*, **254**, 320 (1889).

[185] Krüger and Tollens, *Zeitschrift des Vereins Rübenzucker-industrie*, **1896**, 21; *Chem. Centr.*, **1896**, I, 576.

[186] Komers and Stift, *Oesterr.-ung. Z. Zuckerind.*, **26**, 627 (1897); *Chem. Centr.*, **1897**, II, 644.

[187] Grégoire and Carpiaux, *Bulletin de l'Association belge des Chimistes*, **12**, 143 (1898); *Analyst*, **24**, 39 (1899).

[188] Kröber and Rimbach, *Z. angew. Chem.*, **15**, 477 (1902); **15**, 508 (1902); *Chem. Centr.*, II, 1902, 76.

[189] Ellet and Tollens, *Ber.*, **38**, 492 (1905).

comment is needed here, except to say that over a period of years in these laboratories, numerous analytical determinations on known samples have given results varying from 95 to 110 per cent of the actual concentration of furfural. The method is tedious, requiring about 20 hours for a determination, and is subject to experimental errors apparently beyond the control of the analyst. Temperature during precipitation, standing time prior to filtration, and temperature of drying, all affect the result, probably by altering the composition of the precipitate (see [157, 158, 159, 160, 145, 161, 162, 163, 164, 165]).

In Table 4, comparative analytical results by several different methods are presented. The phloroglucinol values listed there were obtained using Schorger's method,[171] which has been generally adopted as a standard by the Cellulose Division of the American Chemical Society. This method may easily provide for a much larger excess of phloroglucinol than that recommended in the A.O.A.C. procedure, and this may account for the fact that in all these determinations the apparent recovery of furfural was in excess of the theoretical, averaging 106.5 per cent.

Determination with Thiobarbituric Acid. Dox and Plaisance[191] (see also [192]) devised an analytical procedure involving precipitation of furfural with thiobarbituric acid, and weighing the product as furfurylidenemalonylthiourea. The method was used, with varying success by Iddles and Robbins,[151] Bailey,[193, 135] and Kline and Acree[137] among others. The last named workers recommended a modification in the procedure, whereby the excess reagent is removed from the precipitate by washing with 12 per cent hydrochloric acid. This modified technique was adopted by Howells[190] who obtained the variable and unsatisfactorily high analyses listed in Table 4.

The method has many of the disadvantages of the phloroglucinol procedure as was pointed out earlier by Sweeney.[30] Other papers dealing with the use of thiobarbituric acid in estimating furfural include Mackney and Reynolds,[176] Van Reenen,[194] Campbell and Smith,[183] Marshall and Norris,[174] Jayme and Sarten.[132, 195]

Determination with 2,4-Dinitrophenylhydrazine. Analysis for furfural by precipitation with 2,4-dinitrophenylhydrazine would appear to have advantages over the phloroglucinol method. It is much less time-consuming, and under certain conditions in a limited number of tests, has given notably accurate and reproducible results on aqueous solutions of known furfural concentration (column 5, Table 5).

[190] Howells, H. P., The Quaker Oats Company, unpublished work.
[191] Dox and Plaisance, *J. Am. Chem. Soc.*, **38**, 2156 (1916).
[192] van Ekenstein and Blanksma, *Ber.*, **43**, 2355 (1910).
[193] Bailey, *Ind. Eng. Chem., Anal. Ed.*, **8**, 389 (1936).
[194] Van Reenen, *J. S. African Chem. Inst.*, **19**, 19 (1936); *C. A.*, **30**, 4195 (1936).
[195] Jayme and Sarten, *Biochem. Z.*, **312**, 78 (1942); *C. A.*, **37**, 6213 (1943).

TABLE 4. ANALYSIS OF AQUEOUS SOLUTIONS OF PURE FURFURAL BY SEVERAL METHODS[190]

(Results represent the per cent recovery on analyzing samples containing 50 mg. furfural)

Phloroglucinol (p. 300)	Thiobarbituric acid (p. 301)	2,4-Dinitrophenylhydrazine (p. 301)	Bromine methods	
			Hughes-Acree (p. 304)	Kullgren-Tyden (p. 304)
105.42	103.92	—	100.02	—
108.40	102.49	—	99.91	101.45
106.94	103.39	—	98.98	101.77
108.86	104.35	99.33	98.89	101.40
107.11	—	—	100.57	101.14
104.97	103.14	—	101.05	101.39
105.70	102.85	—	99.51	—
106.61	104.13	—	100.62	—
104.17	—	98.83	100.14	—
106.54	—	97.81	100.45	—
—	—	98.88	99.67	—
Average analysis 106.47	103.47	98.71	99.98	101.53

TABLE 5. PER CENT RECOVERY OF FURFURAL FROM A 50 MG. SAMPLE USING 2,4-DINITROPHENYLHYDRAZINE[190]

(Precipitation at different temperatures and standing times)

Reynolds, Osburn and Werkman procedure			Adaptation of Iddles and Jackson method	Same as column 3 using twice as much reagent
room temp. (25-30°C.)	5-10°C.	−5°C.	0°C.	
3 hrs.	2 hrs.	1 hr.	1 hr.	
99.70	99.70	97.82	100.90	—
99.71	100.67	97.75	101.40	—
99.00	97.28	100.46	101.32	—
98.88	98.67	97.36	100.90	—
98.39	99.37	97.91	101.04	—
99.37	99.16	95.39	101.32	—
—	—	—	100.81	100.39
—	—	—	101.44	100.18
—	—	—	100.67	100.18
97.94	98.85	—	—	100.11
98.29	99.06	—	101.59	100.39
98.08	99.62	—	101.99	100.04
Average: 98.82	99.15	97.78	101.22	100.22

Unsatisfactorily low results were obtained (Table 4, column 3; Table 5, column 1) using the Reynolds, Osburn and Werkman[196] modification of Simon's[197] method, wherein precipitation was carried out at room temperature, and the mixture permitted to stand for three hours prior to filtration, washing, drying and weighing. In the opinion of the former workers, this procedure is quantitatively equal to precipitation at 5–10° for two hours, or at 0° for one hour. Average values (compare columns 1 and 2, Table 5) would seem to confirm this observation for two of these conditions which were tested here, but it will be noted that results on individual samples show considerable irregularity, and that this is even more pronounced when the precipitation is done in a freezing mixture (Table 5, column 3). However, in the latter instance, when twice as much reagent was employed (50 ml. rather than 25 ml. as recommended by Reynolds *et al.*[196]), very satisfactory quantitative results were obtained in each instance (Table 5, column 5).

Also included in Table 5 (column 4) are the results which Howells[190] obtained on applying to furfural, the method proposed by Iddles and Jackson[198] for the quantitative estimation of benzaldehyde with 2,4-dinitrophenylhydrazine. They are rather uniformly high, averaging somewhat more than 101 per cent of the theoretical. For additional information on the use of this reagent in determining furfural, reference should be made to Fernandez and de Mingo,[199] Vinals[200] and Barta.[201]

Volumetric Analysis:

Methods Using Bromine. Van Eck[202] attempted to measure furfural with an excess of bromine, subsequently adding potassium iodide and titrating the liberated iodine with thiosulfate. Powell and Whittaker[203] (see also [204, 205, 151, 153]) worked out an essentially similar procedure, whereas Pervier and Gortner[124] proposed the titration of furfural, in aqueous acidic potassium bromide, with potassium bromate until free bromine persists as indicated electrometrically. These methods have been reviewed by Kline

[196] Reynolds, Osburn and Werkman, *Iowa State Coll. J. Sci.*, **7**, 443 (1933).
[197] Simon, *Biochem. Z.*, **247**, 171 (1932); *C. A.*, **26**, 3457 (1932).
[198] Iddles and Jackson, *Ind. Eng. Chem., Anal. Ed.*, **6**, 454 (1934).
[199] Fernandez and de Mingo, *Anales soc. espan. fis. quim.*, **32**, 382 (1934); *C. A.*, **28**, 5541 (1934).
[200] Vinals, *Anal. acad. nac. farm. Madrid*, **1935**, 1; *Anales farm. bioquim., Supl.*, **6**, 84 (1935); *C. A.*, **30**, 239 (1936).
[201] Barta, *Biochem. Z.*, **274**, 212 (1934); *C. A.*, **29**, 1035 (1935).
[202] van Eck, *Chem. Weekblad*, **16**, 1395 (1919); *C. A.*, **14**, 509 (1920).
[203] Powell and Whittaker, *J. Soc. Chem. Ind. London*, **43**, 35 T (1924).
[204] Sasaki, *J. Agr. Chem. Soc. Japan*, **6**, 538 (1930); *C. A.*, **24**, 5670 (1930).
[205] Rosenberger, Rabinovich and Frenkel, *Materialui Vesoyuznuii. Nauch-Issledovatel. Inst. Bumazhoni Tzellyuloznoi Prom.* (*Trans. All-Union Sci. Research Inst. Paper Cellulose Ind.*), **1932**, No. 1, 109; *C. A.*, **28**, 5231 (1934).

and Acree.[137] A related electrometric titration procedure with several refinements has recently been described by Griswold.[206]

The accuracy of a method for estimating furfural with bromine depends, of course, upon the selection of experimental conditions which restrict the reaction to some reproducible molecular ratio. Magistad[207] (see also [208]) showed that the first mole of bromine reacts much more rapidly than the second; that the latter reaction has a high temperature coefficient, becoming especially marked at about 50°. This was also recognized by Hughes and Acree[177] (see also [209, 153]) and Kullgren and Tyden[136] (see also [210]) who developed analytical methods based upon the reaction of furfural and bromine in equimolecular proportions.

Hughes-Acree Method. In this procedure, control of the extent of reaction is achieved by regulation of time and temperature. Using a specially designed flask, potassium bromate is added to a solution of furfural in 3 per cent hydrochloric acid at 0–2° and allowed to react for five minutes, after which time potassium iodide is added. Analysis is completed by titration of the liberated iodine with standard thiosulfate, and comparing the volume of the latter reagent with that required in a blank determination on the reagents.

Results obtained by this method are listed in Table 4. Comparison shows that the Hughes-Acree procedure[177] gives closer to the theoretical recovery than any of the other procedures which were tested by Howells.

Kullgren-Tyden Method. This procedure has met with considerable favor in Europe, but has received comparatively little attention in America. It is similar to the Hughes-Acree method, but specifies reaction at 18–20° in the presence of ammonium molybdate as a catalyst which accelerates reaction of the first mole of bromine, but has no significant effect on the further action of the halogen. While the authors of the method do not include blank determinations, Howells strongly recommends this practice, since otherwise large errors may be introduced.

The method[136] is rather outstanding in reproducibility although the results (Table 4) are slightly higher than the theoretical. Despite this, Howells[190] believes that scarcely any published method offers as much in the way of accuracy, simplicity and speed. He does criticize the relatively small range of sample size, 10–50 mg. furfural. Working at the upper limit of this range, he sets the precision of the method at ±0.3 per cent which is very close to the calculated probable error (± 0.2 per cent), indicating that the analyst has excellent control over the various manipulations involved.

While nearly quantitative on pure furfural, it is obvious that neither these methods, nor any other bromine method[p] can give satisfactory results, when analyzing for furfural in the presence of impurities capable of reacting readily with bromine. Howells[190] has demonstrated that small

[p] The "pyridine sulfate bromide" reagent which Angell[211] has used for the determination of furan, methylfuran and furfuryl alcohol, appears to have little or no effect on negatively substituted furan types, specifically, furfural, furoic acid and furonitrile. He reports acidified potassium bromide-potassium bromate as a brominating agent for furoic acid, but that analysis of furfural with this reagent gives only approximately correct results.

[206] Griswold, Klecka and West, *Ind. Eng. Chem., Anal. Ed.*, **18**, 696 (1946).

percentages of acetaldehyde or formic acid, possible impurities in commercial furfural, do not have any appreciable effect. However, as expected, all furan compounds will react to a greater or lesser extent (see Hughes and Acree[212]), hence analysis for furfural in the presence of other furans is generally impractical, although Hughes and Acree[213] have proposed a differential procedure for determining furfural and 5-methylfurfural in mixtures of these two aldehydes.

Bisulfite Methods. Jolles[214] (see also [215]) worked out an analytical procedure for furfural involving addition of an excess of potassium bisulfite to an alcoholic solution of the aldehyde, and titration with iodine to measure the unreacted bisulfite as proposed earlier by Ripper[216] and Feinberg.[217] The method is difficult to control[218, 219, 220] and has been shown to be highly inaccurate.[221] Parkinson and Wagner[221] proposed modified procedures for overcoming the difficulties, and these were applied to the estimation of furfural by Howells[190] who included determinations by the Jolles method

TABLE 6. IODOMETRIC BISULFITE METHODS[190]

(Per cent recovery of furfural from 50 mg. samples)

Jolles method	Modified Ripper-Feinberg method[221]	Excess iodine method[221]
—	92.36	98.52
—	92.36	99.05
90.15	93.68	101.02
89.82	93.25	101.02

for further comparison. His results (Table 6) show the marked superiority of the so-called "excess iodine" procedure (see also [222]).

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[207] Magistad, *Ind. Eng. Chem., Anal. Ed.*, **5**, 253 (1933).

[208] Hamada and Maekawa, *J. Agr. Chem. Soc. Japan*, **16**, 581 (1940); *C. A.*, **35**, 1728 (1941).

[209] Pedinelli and Pessarelli, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 99; *C. A.*, **35**, 54 (1941).

[210] Savard, Leclercq and Reygrobellet, *Agron. trop. Nogent-sur-Marne*, **2**, 170 (1947); *C. A.*, **41**, 5820 (1947).

[211] Angell, *Analyst*, **72**, 178 (1947).

[212] Hughes and Acree, *Ind. Eng. Chem., Anal. Ed.*, **6**, 292 (1934).

[213] Hughes and Acree, *Ind. Eng. Chem., Anal. Ed.*, **9**, 318 (1937).

[214] Jolles, *Z. anal. Chem.*, **45**, 196 (1906); *Chem. Centr.*, **1906**, I, 1676.

[215] Macheleidt, *Chimie and industrie*, **8**, 1099 (1922); *C. A.*, **17**, 610 (1923).

[216] Ripper, *Monatsh*, **21**, 1079 (1900); *Chem. Centr.*, **1901**, I, 477.

[217] Feinberg, *Am. Chem. J.*, **49**, 87 (1913).

[218] Tolman and Trescott, *J. Am. Chem. Soc.*, **28**, 1619 (1906).

[219] Kerp and Wohler, *Arb. kais. Gesundh.*, **32**, 88 (1910); *C. A.*, **4**, 443 (1910).

[220] Gorokholinskaya, *Zavodskaya Lab.*, **6**, 188 (1937); *C. A.*, **31**, 6138 (1937).

[221] Parkinson and Wagner, *Ind. Eng. Chem., Anal. Ed.*, **6**, 433 (1934).

[222] Kolthoff-Furman, "Volumetric Analysis," Vol. II, pp. 450–452, New York, John Wiley and Sons (1929).

Yet another iodometric procedure has been found to give satisfactory results, and is used frequently in these laboratories, particularly for measuring furfural in the presence of furfuryl alcohol. In this method[223] a number of the variables responsible for the inaccuracies of the Jolles procedure are maintained constant, and the others are compensated for by use of a correction factor. Check results by three separate laboratories gave the following results on pure furfural: 100.20, 101.26 and 100.80 per cent.

The use of acidimetric methods to determine excess bisulfite in systems containing furfural is complicated by the ready dissociation of the aldehyde-bisulfite addition compound, although the equilibrium is reported to remain practically unchanged in strong acid solution.[224] Siggia[225] shows that there is no discernable end-point when attempting to determine furfural by reaction with sodium sulfite and measuring the increase in alkalinity by titration with acid.

$$C_4H_3O{-}CHO + Na_2SO_3 + H_2O \rightleftharpoons C_4H_3O{-}\underset{\displaystyle SO_3Na}{\underset{|}{CHOH}} + NaOH$$

In this reaction, furfural behaves like a ketone in that the equilibrium is largely in favor of free furfural.[225]

Determination with Hydroxylamine. Bryant and Smith[226] developed an improved procedure for determining aldehydes and ketones with hydroxylammonium chloride. The principal modification of earlier methods (see [227]) is the use of pyridine to displace the equilibrium toward quantitative oximation by combining with the liberated hydrochloric acid. The pyridine hydrochloride is titrated with standard sodium hydroxide. The authors of the method report the recovery of furfural as 99.2 ± 0.6 per cent based on two determinations. In Howells' hands[190] the recovery was somewhat higher (100.52, 101.63 and 102.35 per cent on three separate samples containing from 0.80 to 0.85 g. furfural) which he attributed to the greater purity of his furfural. However, he found the end-point very difficult to judge, and concluded that the method was of doubtful value, especially where it is necessary to determine the aldehyde in highly colored solutions. No doubt this difficulty could be largely eliminated by adopting a potentiometric titration.

The oximation procedure described by Angell[211] has not been tested in the laboratories of The Quaker Oats Company.

[223] Dunlop and Trimble, *Ind. Eng. Chem., Anal. Ed.*, **11**, 602 (1939).
[224] Höpner, *Das Papier*, **1**, 102 (1947); *C. A.*, **42**, 3701 (1948).
[225] Siggia, "Quantitative Organic Analysis via Functional Groups," p. 13, New York, John Wiley and Sons (1949).
[226] Bryant and Smith, *J. Am. Chem. Soc.*, **57**, 57 (1935).
[227] Noll, Bolz and Belz, *Papier-Fabr.*, **28**, Tech-wiss. Teil, 565 (1930); *C. A.*, **24**, 5669 (1930).

Colorimetric Methods:

One of the characteristics of furfural is its ability to form color bodies with a wide variety of organic compounds. As early as 1850, Stenhouse[228] observed the formation of a red colored product from furfural and aniline in hydrochloric acid. β-Naphthylamine in acetic acid gives an intense bluish-red color[229]; benzidine-acetic acid reagent produces a blue pigment[230] (see also [231, 232]). Furfural and other aldehydes, as well as sucrose and fructose give a green color in Dische's reaction which involves heating with diphenylamine under controlled conditions of acidity, time and temperature[233] (see also [234, 235]).

Baeyer[236] found that furfural reacted with phenolic compounds in acidic medium with formation of colored products, and Udransky[237, 238] showed that the Molisch reagent for carbohydrates, namely α-naphthol and sulfuric acid, could be used to detect as little as 0.003 mg. furfural by a colorimetric method. In the Molisch test, furfural produces a red-violet pigment having an absorption maximum in the neighborhood of 5400–5500 Å[239] (see also [240]). Ekkert[241] gives a detailed description of the color reactions of furfural and other aldehydes with a variety of phenols.

Indole produces an orange, pyrrole a red, and thiophene a green color when warmed with furfural in acidic medium.[242] Cholic acid gives a red color[243] (see also [244]), and cholesterol and other sterols, also react with furfural on heating in a mixture of sulfuric and acetic acids with formation of color bodies.[245, 246] According to Lapin,[245] the most convenient and sensitive aldehyde test for sterols involves the use of furfural and extraction of the formed pigment with chloroform (see also [247]). Wottering[248] (see

[228] Stenhouse, *Ann.*, **74**, 278 (1850).
[229] Erdmann, *J. prakt. Chem.*, **56**, 143 (1897).
[230] McCance, *Biochem. J.*, **20**, 1111 (1926).
[231] Alekseev, *Sintet Kauchuk*, **1936**, No. 10, 13; *C. A.*, **31**, 6051 (1937).
[232] Korenman and Resnik, *Arch. Hyg. u. Bakt.*, **104**, 344 (1930); *C. A.*, **25**, 2783 (1931).
[233] Stacey, Deriaz, Teece and Wiggins, *Nature*, **157**, 740 (1946).
[234] Votoček and Müller, *Collection Czechoslov. Chem. Communications*, **9**, 120 (1937); *C. A.*, **31**, 4920 (1937).
[235] Sanchez, *Anales asoc. quim. argentina*, **23**, 431 (1925); *C. A.*, **20**, 2300 (1926).
[236] Baeyer, *Ber.*, **5**, 25, 280 (1872).
[237] Udransky, *Z. physiol. Chem.*, **12**, 355 (1888).
[238] Udransky, *Z. physiol. Chem.*, **12**, 377 (1888).
[239] Foulger, *J. Biol. Chem.*, **92**, 345 (1931).
[240] Bredereck, *Ber.*, **64**, 2856 (1931).
[241] Ekkert, *Pharm. Zentralh*, **68**, 563 (1927); *C. A.*, **21**, 4018 (1927).
[242] Fleig, *Compt. rend. soc. biol.*, **65**, 283 (1908); *C. A.*, **3**, 429 (1909),
[243] Mylius, *Z. physiol. Chem.*, **11**, 492 (1887); *Chem. Centr.*, **1887**, 1242.
[244] Woker and Antener, *Helv. Chim. Acta*, **21**, 1345 (1938).
[245] Lapin, *Trudy Uzbekskogo Gosudarst. Univ., Sbornik Trudov Khim.*, **15**, 169 (1939); *C. A.*, **35**, 4389 (1941).
[246] Woker and Antener, *Helv. Chim. Acta*, **22**, 511, 666 (1939).
[247] Levine and Richman, *Proc. Soc. Exptl. Biol. Med.*, **31**, 582 (1934).

also [249]) reports furfural, in the presence of sulfuric acid, as a colorimetric reagent for various alkaloids. Conversely, oxydimorphine in concentrated sulfuric acid appears to be a specific reagent for the aldehyde function, giving a green ring upon addition of furfural or other aldehyde.[250]

Of the numerous compounds which give rise to color with furfural, aniline, xylidine and orcinol have received the most attention from the standpoint of developing analytical methods for the aldehyde. The application of these reagents for this purpose is discussed in some detail in the following paragraphs.

Aniline Salts. Meyer[251] observed that commercial glacial acetic acid developed a red color when treated with aniline, and demonstrated that the product responsible for this color could also be obtained by treating furfural with aniline and acetic acid. Foerster[252] noted that furfural, aniline and hydrochloric acid produced a similar result, and by this means detected furfural in fermented starch, sugar, wine and beer. Aniline and hydrochloric acid is the reagent employed in the official method for analysis of furfural in distilled liquors as prescribed by the A.O.A.C.[144b] (see also [253, 254]). The color reactions of a variety of furan compounds with Shear's aniline and hydrochloric acid reagent are discussed by Levine and Seaman.[255] Günther, de Chalmot and Tollens[62] (see also [256]) used aniline and acetic acid in estimating furfural produced from wine, euxanthic acid, and glycuronic acid. This reagent is reported to detect furfural in concentrations as low as one part in fifty thousand[q],[258, 201] but the sensitivity is dependent upon the pH of the solution. Hughes and Acree[139] recommend pH 3 as optimum for the test. Additional information on the use of aniline salts for detecting or estimating furfural may be found in the following papers: Lindet,[259] Heim,[260] Tolman and Trescott,[218] Lampitt, Hughes and Trace,[261]

[q] Akabori[257] reports a sensitivity of 1 p.p.m. if the furfural-containing solution is first treated with barbituric acid and then with the aniline-acetic acid reagent. Similar sensitivities were noted with 5-methylfurfural and 5-(hydroxymethyl)furfural under the same conditions, each of the three aldehydes giving different shades of color.

[248] Wöttering, *Z. anal. Chem.*, **36**, 410 (1897).
[249] Laves, *Pharm. Ztg.*, **37**, 338 (1892); *Chem. Centr.* **1892**, II, 132.
[250] Breton, *Ann. pharm. franc.*, **3**, 72 (1945); *C. A.*, **40**, 5362 (1946).
[251] Meyer, *Ber.*, **11**, 1870 (1878).
[252] Foerster, *Ber.*, **15**, 230, 322 (1882).
[253] Vagezzi and Haller, *Mitt. Lebensm. Hyg.*, **25**, 39 (1934); *C. A.*, **28**, 3832 (1934).
[254] Mohler and Benz, *Mitt. Lebensm. Hyg.*, **25**, 161 (1934); *C. A.*, **28**, 4273 (1934).
[255] Levine and Seaman, *Biochem. J.*, **27**, 2047 (1933).
[256] de Chalmot, *Am. Chem. J.*, **15**, 21, 276 (1893).
[257] Akabori, *Ber.*, **66**, 139 (1933).
[258] Mohler, *Ann. chim. phys.* (6), **23**, 121 (1891).
[259] Lindet, *Compt. rend.*, **111**, 236 (1890); *Chem. Centr.*, **1890**, II, 498.
[260] Heim, *Z. ges. Brauw.*, **21**, 258 (1898); *Chem. Centr.*, **1898**, II, 146.
[261] Lampitt, Hughes and Trace, *Analyst*, **52**, 260 (1927).

Silin and Silina,[262] Andrews and Milroy,[125] Baerts and Vandewijer,[263] Garratt,[264] Korenman and Resnik,[232] Haupt, Kleinert and Stach.[265]

Following the publication of quantitative procedures by Youngburg and Pucher[266] (see also [142, 201]), Stillings and Browning[267] developed a photocolorimetric method involving the addition of furfural to aniline in acetic acid, storage in the dark at 20° for 55 minutes, and measurement of the light transmittance using a suitable filter at the wave length of minimum transmittance (approximately 5180 Å). The concentration of furfural is estimated by reference to a calibration chart based on the results obtained using solutions of known furfural content. The color bodies formed from 5-methylfurfural and 5-(hydroxymethyl)furfural exhibit practically no absorption at the wave length employed, hence these aldehydes do not interfere with the determination of furfural. The most serious drawback to the method is the instability of the color. However, Duncan,[154] Angell,[211] and more recently, Adams and Castagne,[131] have proposed modified procedures to overcome this difficulty.

Xylidine Salts. In 1877, Schiff[52] reported that furfural could be detected by the red color produced when a test paper, prepared by immersion in a solution of xylidine in acetic acid, was brought in contact with vapors containing the aldehyde. The same reagent, later employed by Udransky[238] (see also [229]), was investigated by Votoček[268] as a possible means of estimating furfural and 5-methylfurfural in mixtures. He concluded that it was not specific for either aldehyde, although Suminokura[150] (see also [269]) reports specificity for furfural in his micro-method for the determination of pentosans, which takes advantage of later spectrophotometric technique. Xylidine-acetic acid reagent is also the basis of an analytical method for furfural described by Aspelund and Klingstedt.[270]

The color produced with the xylidine method is said to be more intense and more stable than that obtained with aniline and acetic acid.[269] However, for several reasons, the latter appears to be the preferred reagent in photometric work.[267]

[262] Silin and Silina, *Z. Ver. deut. Zucker-Ind.*, **83**, 390 (1933); *C. A.*, **28**, 674 (1934).

[263] Baerts and Vanderwijer, *15me Congr. chim. ind.* (Bruxelles, Sept., 1935), **1936**, 922; *C. A.*, **30**, 6229 (1936).

[264] Garratt, *Analyst*, **60**, 369 (1935).

[265] Haupt, Kleinert and Stach, *Mitt. Chem. Forsch.-Inst. Ind. Osterr.*, **1**, 97 (1947); *C. A.*, **42**, 4497 (1948).

[266] Youngburg and Pucher, *J. Biol Chem.*, **61**, 741 (1924).

[267] Stillings and Browning, *Ind. Eng. Chem., Anal. Ed.*, **12**, 499 (1940).

[268] Votoček, *Z. Zuckerind. Böhmen*, **23**, 229 (1899); *Chem. Centr.*, **1899**, I, 642.

[269] Suminokura and Nakahara, *Trans. Tottori Soc. Agr. Sci.*, **1**, 158 (1928); *C. A.*, **23**, 2908 (1929).

[270] Aspelund and Klingstedt, *Finnish Paper and Timber J.*, **1933**, 682; *Chimie and industrie*, **32**, 161 (1934); *C. A.*, **28**, 7007 (1934).

Orcinol. Following Reinitzer's[271] (see also [272]) observations with a variety of carbohydrate materials, Bertrand[273] noted that when a hexose was treated with concentrated hydrochloric acid and orcinol, an orange-red color was produced. He further reported that similar treatment of a five-carbon sugar gave a blue-violet color which he attributed to the intermediate formation of furfural. Bial[274] used the same reagent to detect pentoses in urine, a green coloration representing a positive test.

A sensitive quantitative method for determining furfural is based on the blue-green, and finally blue color formed when a solution containing the aldehyde is treated with prescribed amounts of orcinol-acetic acid solution and ferric chloride-hydrochloric acid solution[275, 276] (see also [133]). The authors of the method report that furfural can be detected in concentrations as low as 4 mg. per liter. A modified procedure has been developed by Farrer[277] whereby up to 0.3 mg. furfural can be determined in fifteen minutes. For the mechanism of the color reaction, see Nozoe.[278]

Miscellaneous Methods:

Mentioned here are analytical procedures of only passing interest or, which for one reason or another, have not received much attention. Most of them are listed under the reagent employed; others under the type of reaction involved.

Hydrazine Sulfate

Monti and Masserizzi.[279]

Phenylhydrazine

Gravimetric procedure: de Chalmot and Tollens,[280] Krug,[281] Stift,[282] Hilger.[283]
Volumetric procedure: Günther, de Chalmot and Tollens,[284] Stone,[285] Flint and Tollens,[286] Mann, Krüger and Tollens,[287] Ling and Nanji.[129]

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[271] Reinitzer, *Z. physiol. Chem.*, **14**, 453 (1890).
[272] Nickel, *Chem. Ztg.*, **14**, 836 (1890).
[273] Bertrand, *Bull. soc. chim.* (*3*), **5**, 932 (1891); (*3*), **6**, 259 (1891).
[274] Bial, *Deut. med. Wochschr.*, **28**, 253 (1902); *Chem. Centr.* **1902**, II, 295.
[275] Fleury and Poirot, *Bull. soc. chim. biol.*, **4**, 252 (1922); *C. A.*, **16**, 4159 (1922).
[276] Yoe, "Photometric Chemical Analysis," Vol. 1, p. 419, New York, John Wiley and Sons (1928).
[277] Farrer, *Australian Chem. Inst. J. and Proc.*, **11**, 186 (1944); *C. A.*, **29**, 254 (1945).
[278] Nozoe, *J. Chem. Soc. Japan*, **57**, 798, 813 (1936); *C. A.*, **31**, 1366 (1937).
[279] Monti and Masserizzi, *Ann. chim. applicata*, **37**, 101 (1947); *C. A.*, **41**, 7310 (1947).
[280] de Chalmot and Tollens, *Ber.*, **24**, 694 (1891).
[281] Krug, *J. Anal. Chem.*, **7**, 68 (1893); *Chem. Centr.*, **1893**, I, 861.
[282] Stift, *Oesterr.-ung. Z. Zuckerind.*, **23**, 925 (1894); *Chem. Centr.*, **1895**, I, 448.
[283] Hilger, *Z. Untersuch. Nahr. u. Genussm.*, **4**, 1141 (1901); *Chem. Centr.*, **1902**, I, 232.
[284] Günther, de Chalmot and Tollens, *Ber.*, **24**, 3575 (1891).
[285] Stone, *Ber.*, **24**, 3019 (1891).
[286] Flint and Tollens, *Ber.*, **25**, 2912 (1892).
[287] Mann, Krüger and Tollens, *Z. angew. Chem.*, **9**, 33 (1896).

Gaseometric procedure based on decomposition of the hydrazone, and measurement of the evolved nitrogen: Grégoire and Carpiaux,[187] Menaul and Dowell.[127]

Semioxamazide

Kerp and Unger,[288] Kremann and Klein.[119]

Barbituric acid

Jager and Unger,[289] Fromherz[290] (see also [291, 167, 292, 146, 67, 132, 195]).

Dimethylbarbituric acid

Akabori.[293, 257] The condensation product is also useful for identification purposes, and Akabori[294] gives the following data:

Aldehyde	m.p. (°C.) of derivatives
furfural	195–196
5-methylfurfural	172–172.5
5-(hydroxymethyl)furfural	181–182
5-(ethoxymethyl)furfural	112.5–113
3-(2-furyl)acrolein	223–224

Diphenylbarbituric acid

Tishchenko and Koshin,[295] Campbell and Smith.[183]

Fehling's solution

Baker and Hulton.[296]

Nessler's reagent

Gros,[297] Goswami and Das-Purkaystha.[298]

Chloramine T

Bionda.[299]

Cannizzaro reaction

Allen and Chattaway.[300] The excess alkali is titrated with standard acid.

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[288] Kerp and Unger, *Ber.*, **30**, 585 (1897).
[289] Jäger and Unger, *Ber.*, **35**, 4440 (1902).
[290] Fromherz, *Z. physiol. Chem.*, **50**, 209, 241 (1906).
[291] Conrad and Reinbach, *Ber.*, **34**, 1339 (1901).
[292] Sieber, *Zellstoff u. Papier*, **2**, 253 (1922); *C. A.*, **17**, 633 (1923).
[293] Akabori, *Proc. Imp. Acad. Tokyo*, **3**, 342 (1927); *C. A.*, **21**, 3185 (1927).
[294] Akabori, *J. Chem. Soc. Japan*, **52**, 601 (1931); *C. A.*, **26**, 5077 (1932).
[295] Tishchenko and Koshkin, *J. Applied Chem. U.S.S.R.*, **7**, 1307 (1934); *C. A.*, **29**, 5775 (1935).
[296] Baker and Hulton, *J. Chem. Soc.*, **111**, 121 (1917).
[297] Gros, *Ann. fals.*, **18**, 39 (1925); *C. A.*, **19**, 1549 (1925).
[298] Goswami and Das-Purkaystha, *J. Indian Chem. Soc.*, **13**, 315 (1936); *C. A.*, 30, 6669 (1936).
[299] Bionda, *Ann. chim. applicata*, **31**, 31 (1941); *C. A.*, **35**, 3558 (1941).
[300] Allen and Chattaway, *Analyst*, **16**, 102 (1891).

Oxidation to furoic acid

(a) Ammoniacal silver oxide is reduced by the aldehyde to metallic silver which is measured by titration with ammonium thiocyanate. Cormack.[301]

(b) Furfural is determined in the presence of ketones by oxidation with silver oxide and titration of the formed acid with standard sodium hydroxide. Mitchell and Smith.[303]

(c) Furfural is oxidized using an excess of iodine in strongly alkaline solution following which the unreacted iodine is determined. Rogers[302] (see also p. 31, of ref. 137).

Chloral hydrate and ammonia

Furfural reacts with reagent to form $C_4H_3O—CH=NCH(OH)CCl_3$, m.p. 129°. By this means it can be detected or separated from aliphatic aldehydes and ketones.[303a]

Ultraviolet spectroscopy

Applied to furfural, 5-methylfurfural and 5-(hydroxymethyl)furfural. Stone and Blundell,[304] Fuchs.[305]

Physical Properties

The data presented in this section have been selected very carefully from the published and available unpublished works concerned either wholly or in part with the physical properties of furfural. A goodly portion of these has been determined independently by several investigators and the values given below are those which appear to have been measured the most accurately. Work performed with equal care by different investigators has led, in some instances, to values which are not concordant. In these cases the data given are those which have been disseminated[306] to industry; however, appropriate reference is made to all original articles concerned. There also are instances where only one report of a particular measurement has been made. The data falling in this category are presented as published, with no attempt to evaluate the accuracy of the work.

Certain physical properties, such as the parachor, dipole moment, magnetic susceptibility, etc., which are useful in elucidating the structure of furfural, are discussed elsewhere (Chapter 1).

General

Molecular weight (theory)	96.082
Appearance (freshly distilled sample)	colorless liquid

[301] Cormack, *Proc. Chem. Soc.*, **16**, 156 (1900); *J. Chem. Soc.*, **77**, 990 (1900).
[302] Rogers, *Ind. Eng. Chem., Anal Ed.*, **16**, 319 (1944).
[303] Mitchell and Smith, *Anal. Chem.*, **22**, 746 (1950).
[303a] Spasov and Ivanov, *Annuaire univ. Sofia, Faculté phys.-mat.*, **43, Livre 2,** 1 (1946–1947); *C. A.*, **44**, 484 (1950).
[304] Stone and Blundell, *Can. J. Research*, B, **28**, 676 (1950).
[305] Fuchs, *Monatsh.*, **81**, 70 (1950); *C. A.*, **44**, 8825 (1950).
[306] The Quaker Oats Company, "Physical Data on Furfural," Bull. 203, 1947.

Odor	pungent, aromatic
Freezing point (°C.)[306, 307, 308, 309]	−36.5
Boiling point (at 760 mm.), °C.[32a, 310, 311, 312]	161.7
Refractive index[r] (n_D^t)	
at 20°C.[310, 313]	1.52608
at 25°C.[314]	1.52345
Density[s] (d_4^t)	
at 20°C.[306, 32a, 313, 318]	1.1598
25°C.[32a, 314, 317]	1.1545
t°C.[317, 319]	$d_4^t = 1.1811(1 - 0.000895t)$
Molecular volume (M/d)[316]	95.52, 95.53
Vapor pressure[306, 310, 312, 320, 321]	see Table 7

The vapor pressures[t] of furfural at various temperatures have been determined by Evans and Aylesworth[310], Curtis and Hatt,[312] Matthews, Sumner and Moelwyn-Hughes[320] and Rae.[321] The values reported by these investigators are collected in Table 7, and have been correlated and a curve representing the best set of values is plotted in Figure 1.

Through analysis of their results (Table 7) by the method of least squares, Matthews *et al.*[320] derived the following equation,

$$\log p_{mm} = 29.3265 - 6.9418 \log T - \frac{3530.52}{T},$$

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[r] For different temperatures and/or wave lengths, see [313, 314, 315].

[s] The density of furfural increases on standing in contact with air[32a] (see also p. 385). The values presented here were determined on freshly distilled samples. For data at other temperatures, see [308, 314, 315, 316, 317].

[t] Vapor pressure values for furfural have also been assigned by Stull.[322] These appear to have been determined by graphical interpolation between a single observation by Walden[323] (b.p. 73° (25 mm.)) and the atmospheric boiling point. In view of the careful determinations reported above, these "assigned" values have not been considered.

[307] Walden, *Z. physik. Chem.*, **73**, 261 (1910).

[308] Jaeger, *Z. anorg. Chem.*, **101**, 1 (1917).

[309] Timmermans, *Bull. soc. chim. Belg.*, **31**, 389 (1922); *C. A.*, **17**, 3014 (1923).

[310] Evans and Aylesworth, *Ind. Eng. Chem.*, **18**, 24 (1926).

[311] Lloyd, Thompson and Ferguson, *Can. J. Research*, **B, 15**, 98 (1937).

[312] Curtis and Hatt, *Australian J. Sci. Research, Ser. A*, **1**, 213 (1948).

[313] Brühl, *Ann.*, **235**, 1 (1886).

[314] Walden, *Z. physik. Chem.*, **59**, 385 (1907).

[315] Kanonnikow, *J. prakt. Chem.*, **31**, 321 (1885).

[316] Schiff, *Ann.*, **220**, 71 (1883).

[317] Walden, *Z. physik. Chem.*, **65**, 129 (1908).

[318] Walden, *Z. physik. Chem.*, **55**, 220 (1906).

[319] Jaeger and Kahn, *Proc. Acad. Sci. Amsterdam*, **18**, 617 (1915); *C. A.*, **10**, 2546 (1916).

[320] Matthews, Sumner and Moelwyn-Hughes, *Trans. Faraday Soc.*, **46**, 797 (1950).

[321] Rae, H. K., Dissertation, Princeton University, 1950.

[322] Stull, *Ind. Eng. Chem.*, **39**, 517 (1947).

[323] Walden, *Z. physik. Chem.*, **70**, 569 (1910).

relating the vapor pressure to the absolute temperature[u]. The simplified formula,

$$\log p_{mm} = 7.959 - \frac{2209}{T},$$

which holds over the range 100 mm. to 6000 mm. of Hg, was presented earlier by Curtis and Hatt[312] when they applied the same method of analysis to their own data and those of Evans and Aylesworth (Table 7).

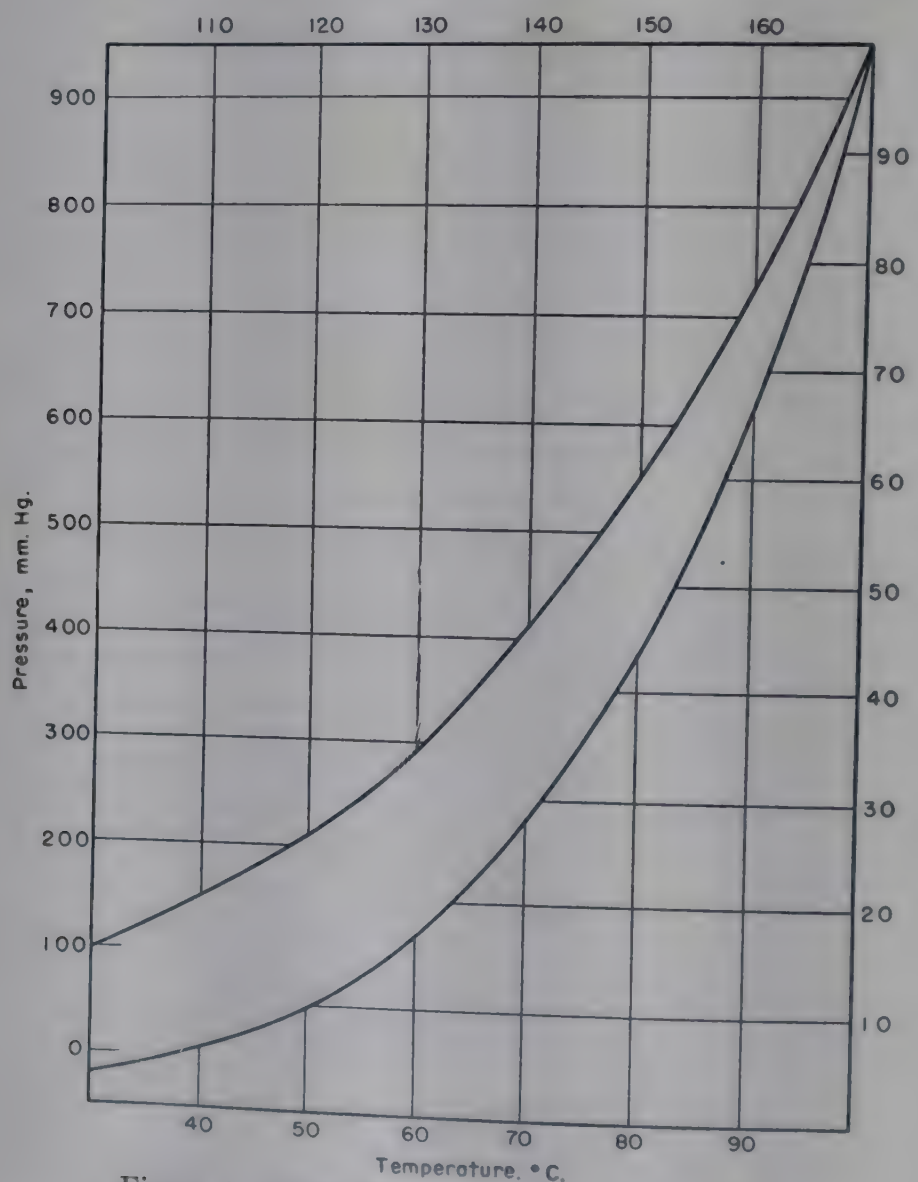


Figure 1. Vapor Pressure Curve for Furfural

[u] It is interesting to note that Matthews and co-workers[320] report the boiling point of furfural at 760 mm. to be 160.7°. The currently accepted value is 161.7°[306, 32a, 310, 312].

[324] Aktiebolaget Tannin, Västervik, Sweden, data sheet on furfural, January, 1946.
[325] Morgan and Stone, *J. Am. Chem. Soc.*, **35**, 1505 (1913).

TABLE 7. VAPOR PRESSURES OF FURFURAL‡

(See Figure 1)

°C.	mm. Hg	°C.	mm. Hg	°C.	mm. Hg
39.9*	8	94.3†	76	135.94	367.1
55.86	13.25	95.4†	81	138.34	399.5
56.06	13.45	96.1†	83	139.94	422.8
64.57	20.90	96.6†	85	140.2*	411
67.69	24.91	96.76	90.46	143.79	462.3
75.04	35.1	97.7†	88	146.84	517.8
75.2†	34	102.12	113.1	149.64	538.0
76.46	37.76	103.30	117.8	151.69	579.4
81.5†	44	105.08	127.6	153.94	618.6
82.3†	46	107.26	137.2	154.4*	625
83.9†	51	111.64	162.4	155.09	641.0
84.3†	52	116.24	185.5	159.0*	707
84.94	54.41	118.39	203.9	160.74	764.2
86.2†	56	120.3*	214	160.9*	744
87.37	61.8	120.84	223.1	161.7*	760
88.9†	61	124.74	256.1	163.8*	812
92.1†	69	126.04	263.0	170.6*	966
92.1†	71	126.34	271.0	223.8§	3357
92.14	74.7	131.6*	310	239.8§	4551
92.3*	69	132.14	326.9	253.8	5777
93.04	77.32	133.79	339.8		

* Evans and Aylesworth.[310] § Curtis and Hatt.[312]

† Rae.[321] ‡ Unless otherwise designated, data are from Matthews, Sumner and Moelwyn-Hughes.[320]

Critical pressure (psia)[324]	798
Critical temperature (°C.)[324, 325]	397
Vapor density (air = 1.00)[326]	3.31
Vapor diffusion coefficient, cm.²/sec.	
at 17°C.[327]	0.076
25°C.[328]	0.087
50°C.[328]	0.107
Flash point (°C.)[306, 326]	
closed cup	60.0
open cup	68.3
Ignition temperature (°C.)[306, 326]	393
Explosive limits (% by vol.)	
lower (at 125°C. and 740 mm.)[329]	2.1
upper	not reported
Molecular association[330]	1.11

[326] Factory Mutual Engineering Division, Loss Prevention Bull. **36.10,** p. 9 (1950).

[327] Pasquill, *Proc. Roy. Soc. London,* **A182,** 75 (1943).

[328] Brookfield, Fitzpatrick, Jackson, Matthews and Moelwyn-Hughes, *Proc. Roy. Soc. London,* **A190,** 59 (1947).

[329] Jones and Klick, *Ind. Eng. Chem.,* **29,** 791 (1929).

[330] Getman, *J. Phys. Chem.,* **29,** 395 (1925).

Viscosity, cps.[318, 331]	
at 0°C.	2.475
25°C.	1.494
Surface tension, dynes/cm.[v]	
at 0°C.[308]	43.5
29.9°C.[308]	40.7
30°C.[332]	41.09
t°C.[325]	$\gamma_t = 44.34 - 0.1221t$
Dielectric constant[306, 323, 333]	
at 1°C.	46.9
25°C.	38
50°C.	34.9

Magnetic

The magnetic susceptibility of furfural is discussed in Chapter 1. For other magnetic properties of this aldehyde, see the original papers of Cotton and Mouton.[334]

Electrical

Electrical absorption index[333]	0.02
Electrical conductivity (at 20°C), mho[335]	1.1×10^{-6}
Specific conductivity, mho[336]	
minimum	0.26×10^{-5}
maximum	0.37×10^{-5}
Electrocapillary function (maximum), mm.[337]	891

Thermodynamic

Heat of combustion (liquid), $\Delta H_{298.16}$, kcal./mole[338, 339, 340, 341]	−560.3
Heat of formation (liquid), $\Delta H_{298.16}$, kcal./mole[338, 339, 341]	−49.2
Heat of fusion, $\Delta H_{235.1}$, kcal./mole[341]	3.43
Heat of vaporization, $\Delta H_{433.8}$, kcal./mole[320, 342]	9.22
Specific heat (liquid), cal./g./deg.	
from 14 to 80°C.[343]	0.401
from 20 to 100°C.[324]	0.416

[v] For values at other temperatures, see [308].

[331] Getman, *J. Am. Chem. Soc.*, **30**, 1077 (1908).
[332] Ray, *J. Indian Chem. Soc.*, **11**, 499 (1934).
[333] Drude, *Z. physik. Chem.*, **23**, 310 (1897).
[334] Cotton and Mouton, *Ann. chim. phys.* (*8*), **19**, 153 (1910); **28**, 209 (1913).
[335] Schmidt, *Z. physik. Chem.*, **75**, 305 (1911).
[336] Walden, *Z. physik. Chem.*, **46**, 103 (1903).
[337] Gouy, *Ann. chim. phys.* (*8*), **8**, 291 (1906); **9**, 75 (1906).
[338] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).
[339] Berthelot and Rivals, *Ann. chim. phys.* (*7*), **7**, 29 (1896).
[340] Middendrop, *Rec. trav. chim.*, **38**, 1 (1919).
[341] Miller, *Iowa State Coll. J. Sci.*, **10**, 91 (1935).
[342] Mathews, *J. Am. Chem. Soc.*, **48**, 562 (1926).
[343] André, *Compt. rend.* **128**, 1035 (1899).

Molar heat capacity (liquid), cal./deg./mole	
from 14 to 80°C.[343]	38.5
from 20 to 100°C.[324]	39.9
Entropy of fusion, $\Delta S_{235.1}$, cal./deg./mole[341]	14.60
Entropy of vaporization, $\Delta S_{433.8}$, cal./deg./mole[341]	21.26
Free energy of formation (liquid), $\Delta F_{298.16}$, kcal./mole[341]	−31.98

Solvent Characteristics

Solubility (see also [344, 306]). Furfural is completely miscible with most of the common organic solvents such as alcohol, ether, acetone, chloroform, and benzene and other aromatic hydrocarbons. It is only slightly miscible with saturated aliphatic hydrocarbons at ordinary temperatures. The solvent action of furfural on a number of organic liquids and solids has been estimated qualitatively by Hammer.[345] A more comprehensive treatment of the solubilities of representative organic compounds in furfural has been presented by Trimble.[344] Hoerr *et al.*[346] have reported the solubility data for several normal saturated fatty acids in furfural.

Inorganic compounds, in general, are quite insoluble in furfural. Exceptions, however, are anhydrous zinc chloride and the hydrates of barium hydroxide and ferric chloride which are soluble to the extent of 10–20 per cent by weight at 25°.[344]

Phase Behavior. In the presence of certain other liquids, furfural exhibits unique solvent properties which have resulted in its widespread use in a variety of separation processes. When furfural is added to a mixture of paraffinic and olefinic compounds it displays a high degree of solvent selectivity for the unsaturated material, thus facilitating a separation which otherwise might have been extremely difficult or impossible to achieve. Vegetable oils and lubricating oils are refined by application of this selective solvent activity to liquid-liquid extractions. The recovery of practically pure butadiene from a mixture of C_4-hydrocarbons and the separation of close-boiling aromatic-nonaromatic, catalytically reformed petroleum cuts are examples of similar solvent selectivity applied through extractive distillation techniques. (For a more detailed discussion of extractions utilizing furfural, see pp. 733–764).

Approximately half of the furfural currently produced finds use in such solvent applications where the recovery of furfural is mandatory in order to make the process economically feasible. Recovery systems for all the processes mentioned above have been developed. On the other hand, lack of knowledge as to the physical properties of liquid systems containing furfural may have been a deterrent to the possible use of furfural in related

[344] Trimble, *Ind. Eng. Chem.*, **33**, 660 (1941).
[345] Hammer, *Chemistry & Industry*, **1933**, 608.
[346] Hoerr, Sedgwick and Ralston, *J. Org. Chem.*, **11**, 603 (1946).

operations. Accordingly, the remainder of this chapter will be devoted to a detailed discussion of the phase behavior of liquid–liquid systems having furfural as one of the components.

Binary Systems. Furfural is generally prepared by treatment of carbohydrate materials with aqueous mineral acids at elevated temperatures. It can be recovered from the resulting aqueous solution by solvent extraction[347] or by steam distillation.[348, 349] The current commercial method of producing furfural entails the digestion of agricultural residues with dilute mineral acid under pressure and recovery of the furfural formed by continuous steam stripping. The procedures employed for the recovery of furfural in commercial solvent-extract applications are similar. Thus, it is evident that the properties of aqueous solutions of furfural are of considerable importance.

Furfural-Water System. Furfural and water are miscible in all proportions above 120.9°; below this temperature a two-phase region exists. Mains[32a] determined the mutual solubilities of furfural and water, but only to the boiling point of the system (97.2° at 760 mm.). The compositions and temperatures of the conjugate liquid phases are given in Table 8.

Table 8. Mutual Solubility of Furfural and Water[32a]

Temp. (°C.)	% Furfural by weight	
	water layer	furfural layer
10	7.9	96.1
20	8.3	95.2
30	8.8	94.2
40	9.5	93.3
50	10.4	92.4
60	11.7	91.4
70	13.2	90.3
80	14.8	88.7
90	16.6	86.5
97.9*	18.4	84.1

* Boiling point at 760 mm.

Rothmund,[350] and Evans and Aylesworth[310] investigated the mutual solubilities of furfural and water in relation to their critical solution point. The data obtained by Evans and Aylesworth agree with those of Mains[32a] but disagree with Rothmund's. A redetermination of the solubility curve of furfural and water by Curtis and Hatt[312] resulted in close confirmation

[347] Trimble and Dunlop, *Ind. Eng. Chem., Anal Ed.*, **12**, 721 (1940).
[348] Lewis (to Standard Oil Development Co.) U. S. Pat. 1,911,832 (1933); *C. A.*, **27**, 3999 (1933).
[349] Smoley and Kraft, *Ind. Eng. Chem.*, **27**, 1418 (1935).
[350] Rothmund, *Z. physik. Chem.*, **26**, 433 (1898).

of the findings of Evans and Aylesworth. The critical solution temperature was found[310] to be 120.9°, and the critical solution concentration, 50.7 per cent furfural by weight. The solution temperatures of the furfural-water system are presented in Table 9. Curves for the solution temperature of the system[310] and as influenced by metal sulfates[312] are given in Figure 2.

TABLE 9. SOLUTION TEMPERATURE OF FURFURAL-WATER SYSTEM[310]

Furfural wt. (%)	Temp. (°C.)
9.03	39.5
9.82	53.1
15.04	85.8
20.75	102.8
22.39	106.1
27.84	113.1
33.77	117.9
47.37	120.8
48.98	120.85
50.30	120.9
50.4	120.0
50.54	120.9
50.69	120.85
56.34	120.5
65.03	119.15
72.19	115.1
83.03	95.95
88.79	73.6
91.83	53.35
94.9	27.85

In establishing the phase diagram for the furfural-water system, Mains[32a] constructed a comprehensive composition-density table in order to determine accurately the composition of the liquid and vapor phases. These data are reproduced in Tables 10 and 11. A complete phase diagram at atmospheric pressure over the range 10 to 160° is presented in Figure 3.

Furfural and water form a non-ideal binary system. At atmospheric pressure, water and furfural form a minimum-boiling heteroazeotrope containing 35 per cent furfural by weight and boiling at 97.9°[32a]. Curtis and Hatt[312] found that at 87.7 and 111.7 psia, homoazeotropes of practically the same composition existed. At these increased pressures, there is no evidence of any tendency for the binary system to change from the minimum-boiling type.

Pearce and Gerster[351] determined the isothermal vapor-liquid equilibrium relationships for the furfural-water system at 100, 150 and 200°F., tem-

[351] Pearce and Gerster, *Ind. Eng. Chem.*, **42**, 1418 (1950).

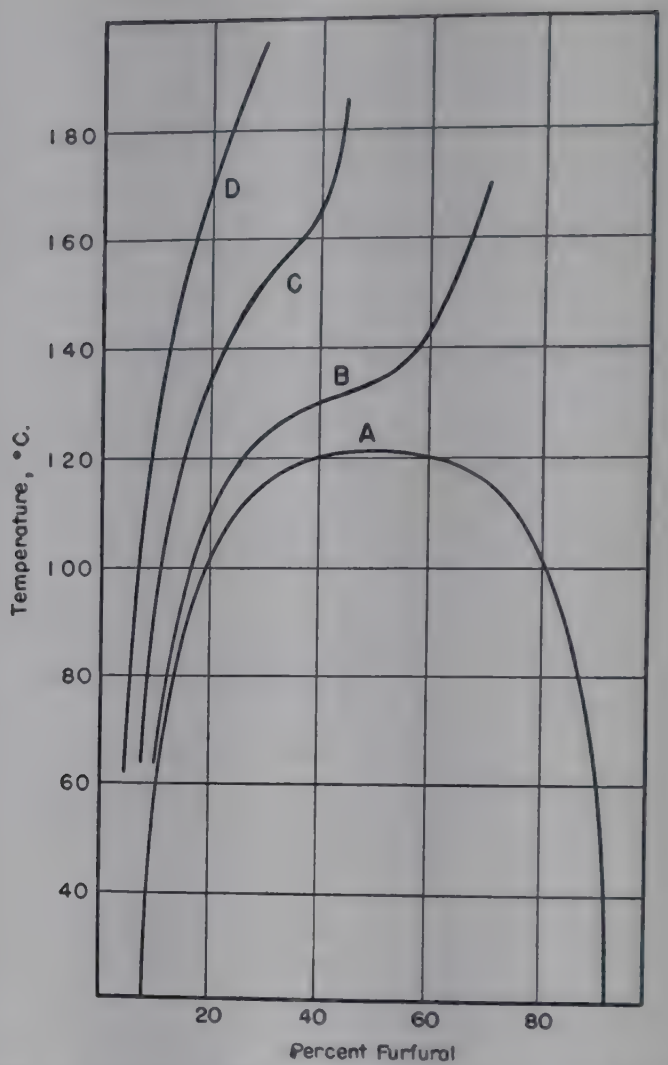


Figure 2. Curves for Solution Temperatures of Furfural-Water Systems.[312]
(A) Furfural and distilled water.
(B) Furfural and 1.168 per cent Na_2SO_4 solution.
(C) Furfural and 5.016 per cent Na_2SO_4 solution.
(D) Furfural and 10.00 per cent Na_2SO_4 solution.

peratures of interest in extractive distillation processes. From these data, they calculated the activity coefficients and partial heats of solution.

Other Binary Systems. The recovery of furfural from non-aqueous binary mixtures may be accomplished by flash vaporization, straight distillation, azeotropic distillation, extractive distillation or solvent extraction. The method applied generally depends on the phase behavior of the constituents in the binary system. Similarly, the proper design and economic operation of distillation equipment requires adequate knowledge of the phase equilibrium involved.

A comprehensive study of the phase equilibria in furfural-hydrocarbon systems, together with their thermodynamic analysis has been performed only recently by Rae.[321] In his thesis are correlated all the available critical solution temperatures of furfural with hydrocarbons. A correlation of the azeotropes which furfural forms with aromatic hydrocarbons is also pre-

TABLE 10. COMPOSITION-DENSITY OF FURFURAL-WATER SYSTEM[32a]

Wt. % furfural	Density t/4°C. 20°C.	25°C.
0	0.9982	0.9971
0.2	0.9986	0.9974
0.4	0.9990	0.9978
0.6	0.9993	0.9982
0.8	0.9997	0.9985
1.0	1.0001	0.9989
1.2	1.0005	0.9993
1.4	1.0008	0.9996
1.6	1.0012	1.0000
1.8	1.0016	1.0003
2.0	1.0020	1.0007
2.2	1.0023	1.0011
2.4	1.0027	1.0014
2.6	1.0031	1.0018
2.8	1.0034	1.0022
3.0	1.0038	1.0025
3.2	1.0042	1.0029
3.4	1.0046	1.0033
3.6	1.0049	1.0036
3.8	1.0053	1.0040
4.0	1.0057	1.0044
4.2	1.0060	1.0047
4.4	1.0064	1.0051
4.6	1.0068	1.0054
4.8	1.0072	1.0058
5.0	1.0075	1.0062
5.2	1.0079	1.0065
5.4	1.0083	1.0069
5.6	1.0086	1.0073
5.8	1.0090	1.0076
6.0	1.0094	1.0080
6.2	1.0098	1.0084
6.4	1.0101	1.0087
6.6	1.0105	1.0091
6.8	1.0109	1.0094
7.0	1.0113	1.0098
7.2	1.0116	1.0102
7.4	1.0120	1.0105
7.6	1.0124	1.0109
7.8	1.0127	1.0113
8.0	1.0131	1.0116
8.2	1.0135	1.0120
8.3*	1.0137	1.0122
8.4	—	1.0124
8.6†	—	1.0127

* Saturated solution of furfural in water at 20°C.

† Saturated solution of furfural in water at 25°C.

TABLE 11. VAPOR-LIQUID EQUILIBRIA IN THE FURFURAL-WATER SYSTEM[352a]

(Pressure = 760 mm.)

% Furfural by wt. composition of solution	composition of distillate	B.p. (°C.)
0.2	1.5	99.90
0.4	3.0	99.82
0.6	4.4	99.74
0.8	5.8	99.67
1.0	7.0	99.60
1.5	10.0	99.42
2.0	12.7	99.25
2.5	15.0	99.11
3.0	17.1	98.99
3.5	19.0	98.87
4.0	20.7	98.76
4.5	22.2	98.66
5.0	23.6	98.58
5.5	24.8	98.50
6.0	25.8	98.43
6.5	26.8	98.37
7.0	27.7	98.31
7.5	28.5	98.26
8.0	29.2	98.21
8.3*	29.6	98.19
8.5	29.9	98.17
9.0	30.5	98.13
10.0	31.7	98.07
11.0	32.6	98.02
12.0	33.3	97.98
13.0	33.9	97.95
14.0	34.4	97.93
15.0	34.7	97.92
16.0	34.8	97.91
17.0	34.9	97.91
18.0	35.0	97.90
18.4†	35.0	97.90
18.4–84.1‡	35.0	97.90

* Saturated solution of furfural in water at 20°C.
† Saturated solution of furfural in water at the boiling point.
‡ Range over which both furfural and water layers are present.

sented. Furfural solution temperatures of hydrocarbons have also been reported by Rice and Lieber,[352] and Schiessler *et al.*[353]

Vapor-liquid equilibria and thermodynamic properties of binary mixtures of *n*-butane, isobutane and 1-butene with furfural are interpreted by Mertes and Colburn.[354] Other vapor-liquid equilibria reported are:

[352] Rice and Lieber, *Ind. Eng. Chem., Anal. Ed.*, **16**, 107 (1944).
[353] Schiessler *et al.*, *Proc. Am. Petroleum Inst.*, **III**, 26, 254 (1946).
[354] Mertes and Colburn, *Ind. Eng. Chem.*, **39**, 787 (1947).

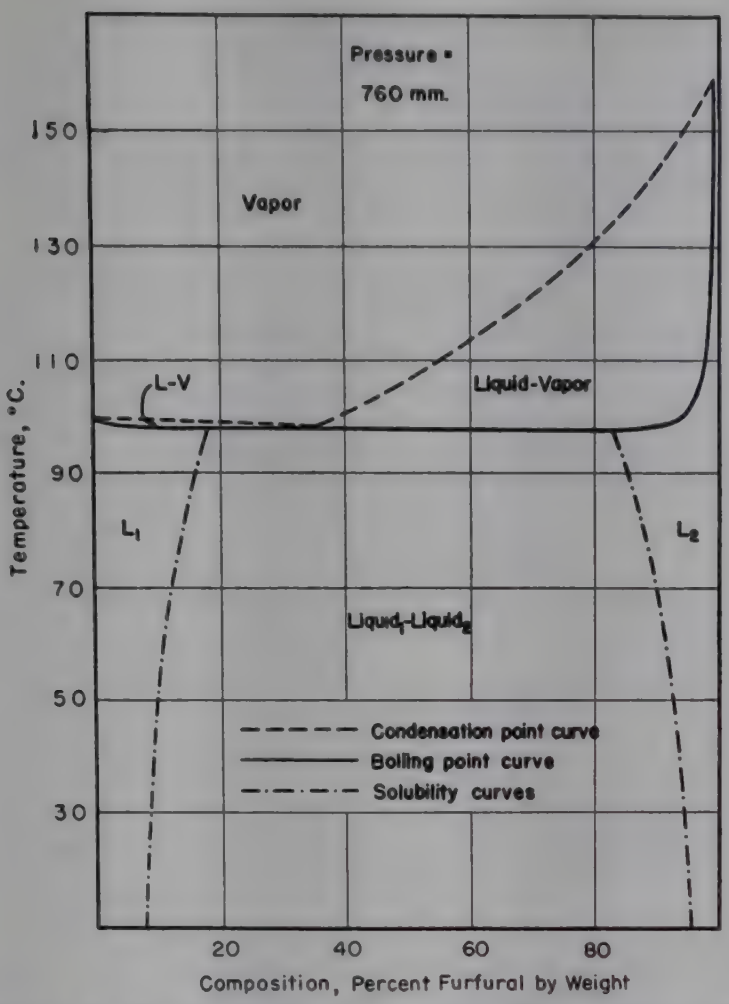


Figure 3. Phase Diagram—Furfural-Water System.[32a]

furfural-acetic acid[355]; furfural-acetaldehyde[355]; furfural-furfuryl alcohol,[356] and furfural–2-methylfuran.[357]

Complete phase equilibria data for non-aqueous furfural binaries are too numerous to present here. However, in Table 12 are listed furfural-hydrocarbon critical solution temperatures and concentrations, together with references to the original literature. Furfural-hydrocarbon binary azeotropes are collected in Table 13, and other azeotropes containing furfural are presented in Table 14.

Multicomponent Systems. The use of wet furfural as the extracting agent in the extractive distillation of C_4-hydrocarbon mixtures for butadiene recovery has led to a comprehensive study of the various binary and ternary systems involved. Attempts have been made to correlate experimentally obtained activity coefficients with theoretical equations expressing the change of activity coefficients with temperatures, pressure and composition. In general, the correlation has been sufficiently good to warrant prediction of vapor-liquid equilibria for the more complex systems actually existing.

[355] Othmer, *Ind. Eng. Chem.*, **35**, 614 (1943).
[356] Dunlop and Trimble, *Ind. Eng. Chem.*, **32**, 1000 (1940).
[357] Holdren and Hixon, *Ind. Eng. Chem.*, **38**, 1061 (1946).

TABLE 12. FURFURAL-HYDROCARBON CRITICAL SOLUTION TEMPERATURES AND CONCENTRATIONS

Hydrocarbon	Critical soln. temp. (°C.)	Critical soln. concn. (mole fraction of furfural)	Ref.
Paraffins			
C_6H_{14}			
n-Hexane	90.7, 92	0.514	321, 358
2-Methylpentane	94.0	0.518	321
3-Methylpentane	89.2	0.507	321
2,2-Dimethylbutane	97.3	0.512	321
2,3-Dimethylbutane	89.5	0.510	321
C_7H_{16}			
n-Heptane	95.3, 95	0.605	321, 359
2,3-Dimethylpentane	89.5	0.504	321
2,4-Dimethylpentane	98.7, 98	0.485	321, 359
C_8H_{18} and C_9H_{20}			
n-Octane	96.9	0.610	321
2-Methylheptane	101	—	358
2,2,4-Trimethylpentane	99.4, 90	0.541	321, 359
2,2,5-Trimethylhexane	106.3	0.603	321
$C_{10}H_{22}$ to $C_{14}H_{30}$			
n-Decane	104.8	0.673	321
n-Dodecane	109.3, 112.5	0.720	321, 353
n-Tridecane	115.9	—	353
n-Tetradecane	119.6	—	353
7-Methyltridecane	118.5	—	353
$C_{15}H_{32}$ to $C_{19}H_{40}$			
n-Pentadecane	122.7	—	353
n-Hexadecane	122.9, 125.9	0.785	321, 353
n-Heptadecane	129.2	—	353
n-Octadecane	131.9	—	353
7-Hexyltridecane	132.2	—	353
$C_{20}H_{42}$ to $C_{25}H_{52}$			
n-Eicosane	138.1	—	353
4-Propylheptadecane	130.9	—	353
5-Butylhexadecane	134.6	—	353
n-Docosane	144.0	0.820	360
9-Hexylheptadecane	141.7	—	353
n-Tetracosane	147.2	—	353
9-Octylheptadecane	146.4	—	353
$C_{26}H_{54}$			
n-Hexacosane	150.3	—	353
3-Ethyltetracosane	149.2	—	353
5-Butyldocosane	148.0	—	353

TABLE 12—*Continued*

Hydrocarbon	Critical soln. temp. (°C.)	Critical soln. concn. (mole fraction of furfural)	Ref.
Paraffins—*continued*			
$C_{26}H_{54}$			
7-Butyldocosane	148.0	—	353
9-Butyldocosane	148.1	—	353
11-Butyldocosane	147.9	—	353
11-Pentylheneicosane	147.6	—	353
11-(1′-Ethylpropyl)heneicosane	146.2	—	353
11-(2′,2′-Dimethylpropyl)heneicosane	146.3	—	353
7-Hexyleicosane	147.7	—	353
3-Ethyl-5-(2′-ethylbutyl)octadecane	144.5	—	353
5,14-Dibutyloctadecane	145.7	—	353
6,11-Dipentylhexadecane	145.6	—	353
$C_{27}H_{56}$ to $C_{32}H_{66}$			
7-Hexyldocosane	151.3	—	353
9-Octyleicosane	151.7	—	353
9-Octyldocosane	150.9	—	353
11-Decylheneicosane	154.0	—	353
11-Decyldocosane	157.7	—	353
Olefins			
2-Pentene	16.2	0.476	321
1-Hexene	48.6	0.470	321
1-Heptene	56	—	358
1-Octene	60.9	0.570	321
2-Octene	61.0	0.592	321
2,2,4-Trimethyl-2-pentene	62	—	358
1-Dodecene	84.0	0.711	321
1-Tridecene	91.8	—	353
1-Pentadecene	100.3	—	353
1-Heptadecene	108.6	—	353
1-Octadecene	111.5	0.790	321
9-Octyl-8-heptadecene	124.5	—	353
Cyclics			
Methylcyclopentane	65.2	0.435	321
Cyclohexane	65.0, 69	0.447	321, 358
Methylcyclohexane	73.3, 76	0.498	321, 358
1-Methyl-4-(1′-methylethene-1′-yl)cyclohexene-1 (*dl*-limonene)	23.9	0.663	321
1-Cyclohexyloctane	110.7	—	353
2-Cyclohexyloctane	108.5	—	353
1-(2′-Methyl-5′-isopropylcyclohexyl)dodecane	135.5	—	361
2,8-Dimethyl-5-(2′-methyl-5′-isopropylcyclohexylmethyl)nonane	132.5	—	361

TABLE 12—*Continued*

Hydrocarbon	Critical soln. temp. (°C.)	Critical soln. concn. (mole fraction of furfural)	Ref.
Cyclics—*continued*			
9-Cyclohexylheptadecane	136.5	—	353
9-(3′-Cyclopentylpropyl)heptadecane	141.5	—	353
9-(2′-Cyclohexylethyl)heptadecane	141.9	—	353
1-Cyclopentylheneicosane	147.7	—	353
11-Cyclopentylheneicosane	143.5	—	353
1-Cyclohexyleicosane	148.2	—	353
2-Cyclohexyleicosane	146.5	—	353
3-Cyclohexyleicosane	145.1	—	353
4-Cyclohexyleicosane	145.0	—	353
5-Cyclohexyleicosane	144.5	—	353
7-Cyclohexyleicosane	144.1	—	353
9-Cyclohexyleicosane	144.1	—	353
8-(4′-Methylcyclohexyl)nonadecane	143.5	—	353
11-Cyclopentylmethyl)heneicosane	146.0	—	353
11-Cyclohexylheneicosane	146.8	—	353
11-(Cyclohexylmethyl)heneicosane	145.9	—	353
13-Cyclohexylpentacosane	153.3	—	353
Methyldiisopropylbenzene	−18	—	358
1-Phenyloctane	10.8	—	353
2-Phenyloctane	7.0	—	353
Diamylbenzene	47	—	358
7-Phenyltridecane	59.8	—	353
1-(2′-Methyl-5′-isopropylphenyl) dodecane	61.3	—	361
9-*p*-Tolyloctadecane	96.0	—	353
9-(2′-Phenylethyl)heptadecane	85.2	—	353
1-Phenyleicosane	95.8	—	353
2-Phenyleicosane	94.8	—	353
3-Phenyleicosane	97.5	—	353
4-Phenyleicosane	96.5	—	353
5-Phenyleicosane	96.4	—	353
7-Phenyleicosane	96.4	—	353
9-Phenyleicosane	97.8	—	353
8-*p*-Tolylnonadecane	100.6	—	353
11-Phenylheneicosane	101.3	—	353
11-Phenylheneicosene-10	84.0	—	353
11-Benzylheneicosane	97.7	—	353
13-Phenylpentacosane	112.6	—	353
1-Cyclopentyl-4-(3′-cyclopentylpropyl)-dodecane	137.5	—	353
1-Cyclopentyl-2-hexadecylcyclopentane	143.1	—	353
1-Cyclohexyl-3-cyclopentylpropane	103.5	—	353
1,1-Dicyclohexylethane	100.7	—	353
1,2-Dicyclohexylethane	104.8	—	353
1,1-Dicyclohexylheptane	122.2	—	353

TABLE 12—*Continued*

Hydrocarbon	Critical soln. temp. (°C.)	Critical soln. concn. (mole fraction of furfural)	Ref.
Cyclics—*continued*			
1,2-Di(2′-methyl-5′-isopropylcyclohexyl)-ethane	126.5	—	361
1-Cyclohexyl-3-(2′-cyclohexylethyl)-undecane	139.6	—	353
1,1-Dicyclohexyltetradecane	141.8	—	353
1,1-Di(4′-methylcyclohexyl)dodecane	139.5	—	353
1-Cyclohexyl-2-(cyclohexylmethyl)pentadecane	146.3	—	353
1-Phenyl-3-cyclopentylpropane	−4.6	—	353
1-Phenyl-1-cyclohexylethane	−4.5	—	353
1-Phenyl-2-cyclohexylethane	−6.1	—	353
1-Phenyl-3-(2′-phenylethyl)undecane	10.5	—	353
1,1-Diphenyltetradecane	4.8	—	353
1,1-Di-*p*-tolyldodecane	19.2	—	353
1-α-Decalin-2-(2′-methyl-5′-isopropylcyclohexyl)ethane	126.5	—	361
1-α-Decalindodecane	130.5	—	361
11-α-Decalinheneicosane	150.3	—	353
α-Hexadecylhydrindene	85.8	—	353
α-Hexadecylhydrindane	141.9	—	353
1,7-Dicyclopentyl-4-(3′-cyclopentylpropyl)heptane	135.5	—	353
1,7-Dicyclopentyl-4-(2′-cyclohexylethyl)-heptane	136.6	—	353
1,5-Dicyclohexyl-3-(3′-cyclopentylpropyl)pentane	137.7	—	353
1,5-Dicyclohexyl-3-(2′-cyclohexylethyl)-pentane	139.1	—	353
1,5-Dicyclohexyl-3-(2′-cyclohexylethyl)-pentene-2	121.0	—	353
1,7-Dicyclopentyl-4-(2′-phenylethyl)-heptane	78.5	—	353
1-Phenyl-3-(2′-cyclohexylethyl)-6-cyclopentylhexane	84.8	—	353
1,5-Diphenyl-3-(3′-cyclopentylpropyl)-pentane	1.5	—	353
9-Dodecylperhydroanthracene	140.1	—	353
9-Dodecylperhydrophenanthrene	141.9	—	353

TABLE 13. HYDROCARBON-FURFURAL BINARY AZEOTROPES

Hydrocarbon	Temp. (°C.)	Pressure (mm. Hg)	Concentration (mole fraction of furfural)	Ref.
n-Heptane	98.2	760	0.040	321
n-Octane (none)	—	—	—	362
2,2,4-Trimethylpentane	97.9	760	0.055	321
2,2,5-Trimethylhexane	123.7	823	0.251	321
2,2,5-Trimethylhexane	80.0*	193	0.210	321
2,2,5-Trimethylhexane	70.0*	135	0.198	321
2,2,5-Trimethylhexane	60.0*	91	0.186	321
2,2,5-Trimethylhexane	50.0*	59	0.174	321
n-Decane	100.0*	143	0.628	321
n-Decane	90.0*	97	0.622	321
n-Decane	80.0*	65	0.619	321
n-Decane	70.0*	43	0.613	321
2,7-Dimethyloctane	150.0	760	0.517	362
n-Dodecane	90.0*	68	0.887	321
n-Dodecane	80.0*	44	0.875	321
n-Dodecane	70.0*	29	0.860	321
Methylcyclohexane	100.2	765	0.038	321
Benzene (none)	—	—	—	321
Toluene (none)	—	—	—	321
p-Xylene	137.9	760	0.115	321
p-Xylene	138.0	760	0.055	362, 363
p-Xylene	100.0	241	0.075	321
m-Xylene	138.65	760	0.102	321
m-Xylene	138.4	760	0.131	362, 363
o-Xylene	140.5	760	0.141	362, 363
Ethylbenzene	136.1	760	0.060	321
n-Propylbenzene	151.4	760	0.438	321
n-Propylbenzene	152.0	760	0.455	362, 363
Isopropylbenzene	147.3	760	0.329	321
1,3,5-Trimethylbenzene	155.2	760	0.652	362, 363
1,2,4-Trimethylbenzene	156.0	760	0.652	362, 363
p-Cymene	158.3	760	0.714	321
p-Cymene	157.8	760	0.748	362, 364
p-Cymene	120.0	238	0.685	321
n-Butylbenzene	158.9	760	0.800	321
n-Butylbenzene	160.5	760	0.864	362, 363
sec.-Butylbenzene	157.3	760	0.708	321
tert.-Butylbenzene	155.9	760	0.608	321
Styrene	141.6	760	0.160	362, 364
α-Pinene	153.0	760	—	362, 363
α-Pinene	143.0	760	0.465	362, 364
Camphene	146.8	760	0.485	362, 364
β-Pinene	146.3	760	0.586	362, 363
p-Menthadiene-1,3	154.5	760	0.632	362, 363
Carvene	156.0	760	0.725	362, 364
Thymene	158.5	760	0.784	362, 364
p-Menthadiene-1,4	160.3	760	0.850	362, 363

* A heterogeneous azeotrope; the liquid consists of two phases.

TABLE 14. BINARY AZEOTROPES WITH FURFURAL

Other component	B.p. °C (760 mm.)	Furfural wt. (%)	Ref.
Anisole	153.25	22	365
Bromobenzene	153.3	30	366
Camphene	146.65	42	367
Carvene	155.95	65	365
o-Chlorotoluene	155.2	*ca.* 32	368
p-Chlorotoluene	157.8	*ca.* 45	368
Cineole	157.25	59	369
Cyclohexanol	155.55	*ca.* 55	367
Cymene	157.8	68	370
p-Dichlorobenzene	160.3	64.5	371
2,7-Dimethyloctane	150	42	370
Mesitylene	155.2	60	366
Pentachloroethane	155.15	50?	367
α-Pinene	143.4	*ca.* 38	367
Styrene	141.0	*ca.* 15	370
Thymene	158.5	72	370
m-Xylene	138.4	12	370
Water	97.9	35	32a

Ternary Systems. The following ternary systems have been investigated and their vapor-liquid equilibria data reported: *n*-butane–1-butene–furfural[372]; isobutane–1-butene–furfural[372]; isobutane–water–furfural[373]; and 1-butene–water–furfural.[373]

Liquid-liquid phase equilibria have been reported for the ternary systems: acetaldehyde–water–furfural[374]; acetone–water–furfural[311, 375]; isoamyl acetate–water–furfural[311]; ethyl acetate–water–furfural[311, 347]; toluene–water–furfural[376]; and docosane–1,6-diphenylhexane–furfural.[360]

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[358] Francis, *Ind. Eng. Chem.*, **36**, 1096 (1944).
[359] Francis, "Physical Chemistry of Hydrocarbons," Vol. I, Chap. 7, New York, Academic Press (1950).
[360] Briggs and Comings, *Ind. Eng. Chem.*, **35**, 411 (1943).
[361] Neyman-Pilat, *Nafta*, **3**, 204 (1947); *C. A.*, **43**, 3602 (1949).
[362] Perry, "Chemical Engineers' Handbook," 3rd Ed., pp. 637–641, New York, McGraw-Hill Book Co. (1950).
[363] Lecat, "La Tension de vapeur des mélanges de liquides, L'Azeotropisme," Bruxelles (1918).
[364] Timmermans, "Les Solutions concentrées," Paris, Masson et Cie. (1936).
[365] Lecat, *Ann. soc. sci. Bruxelles*, **45**, 284 (1926); *C. A.*, **22**, 3561 (1928).
[366] Lecat, *Rec. trav. chim.*, **45**, 520 (1926).
[367] Lecat, *Ann. soc. sci. Bruxelles*, **45**, 169 (1926); *C. A.*, **22**, 3561 (1928).
[368] Lecat, *Ann. soc. sci. Bruxelles*, **47, B, 1**, 108 (1927); *C. A.*, **22**, 1712 (1928).
[369] Lecat, *Compt. rend.*, **222**, 733 (1946).
[370] Lecat, *Ann. soc. sci. Bruxelles*, **47, B, I**, 63 (1927); *C. A.*, **22**, 4296 (1928).
[371] Lecat, *Ann. soc. sci. Bruxelles*, **47**, 21 (1927); *C. A.*, **22**, 3562 (1928).
[372] Gerster, Mertes and Colburn, *Ind. Eng. Chem.*, **39**, 797 (1947).
[373] Jordan, Gerster, Colburn and Wohl, *Chem. Eng. Progress*, **46**, 601 (1950).
[374] Othmer and Tobias, *Ind. Eng. Chem.*, **34**, 690 (1942).
[375] Othmer, White and Trueger, *Ind. Eng. Chem.*, **33**, 1240 (1941).
[376] Knight, *Trans. Am. Inst. Chem. Engrs.*, **39**, 439 (1943).

Holloway and Thurber[377] have determined vapor pressures and liquid densities at 100, 150, 200 and 250°F. in the following ternary systems: *n*-butane–water–furfural (see also [378]); isobutane–water–furfural; 1-butene–water–furfural; and 1,3-butadiene–water–furfural. They also report cloud point data for the first three of these systems.

Michaels, Alexander and Becker[379] have measured refractive indices and surface tensions in the system: toluene–isopropyl alcohol–furfural.

Quaternary Systems. To date, only three quaternary systems containing furfural have been reported; namely, isobutylene–butadiene–naphtha–furfural[380]; isobutane–1-butene–water–furfural[373]; and *n*–butane–*cis*-2-butene–water–furfural.[381]

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[377] Holloway and Thurber, *Ind. Eng. Chem.*, **36,** 908 (1944).
[378] Griswold, Klecka and West, *Chem. Eng. Progress*, **44,** 839 (1948).
[379] Michaels, Alexander and Becker, *Ind. Eng. Chem.*, **42,** 2332 (1950).
[380] Smith and Braun, *Ind. Eng. Chem.*, **37,** 1047 (1945).
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Chapter 9

FURFURAL—CHEMICAL PROPERTIES

Introduction

As a quick means of estimating its potentialities, furfural has often been compared with benzaldehyde, and this type of reasoning by analogy has led the way for a good deal of constructive work on its chemical behavior. However, it is important to recognize that furfural possesses certain individual characteristics, which in a given reaction, may modify or completely alter the course.

As an aldehyde, of course, furfural takes part in the typical reactions of the formyl group, but in many instances, the highly reactive furan nucleus introduces complexities: secondary reactions which in some cases become the major course of reaction. A few examples will serve, at this point, to illustrate the occurrence of such abnormalities.

Under the influence of alkali cyanides, furfural is dimerized to furoin (p. 479), but unlike the analogous formation of benzoin from benzaldehyde, the former reaction invariably involves the simultaneous formation of a large amount of by-product material of unknown composition. The Cannizzaro reaction of furfural (p. 379) is also complicated by a competitive side-reaction giving rise to a highly colored by-product(s). Though incompletely elucidated, the competing reaction(s) in these instances probably involves a nucleophilic attack by the reagent on the furan ring, with subsequent rupture to reactive, open-chain products (see Chapter 14). During the autoxidation of furfural (p. 385), the nucleus is the major point of attack, so that the course of reaction is quite unrelated to what would have been predicted on the basis of the known behavior of benzaldehyde. Thus it is that furfural may not always be substituted indiscriminately for another aldehyde.

General

As expected, furfural forms addition compounds or complexes with a variety of substances. The alkali bisulfite complex is discussed elsewhere (p. 378). An equimolecular addition product is also obtainable by adding potassium hydroxide pellets to furfural in dry ether.[1] Complexes with the Friedel-Crafts type catalysts, aluminum chloride,[2] stannic chloride,[3] and

[1] Dehn and Merling, *J. Am. Chem. Soc.*, **39**, 2646 (1917).
[2] Gangloff and Henderson, *J. Am. Chem. Soc.*, **39**, 1420 (1917).
[3] Pfeiffer, *Ann.*, **376**, 285 (1910).

ferric chloride[2] have been isolated, as have addition compounds of furfural with mercuric chloride[4, 5] (see also [6]), cadmium chloride,[7] and magnesium bromide.[8] Duprat[9] (see also [10]) describes addition compounds of furfural with ferro- and ferricyanic acids, and Adams and Vollweiler[11] have isolated an unstable double compound, $C_{12}H_8O_6Br_2$, m.p. 76–77°, by the action of oxalyl bromide on furfural.

Alkyl- and aryl-magnesium halides and metal acetylides also react with furfural to give additive compounds which are decomposed by water to give the expected carbinols (p. 253). Zinc alkyls[12] add similarly, and the typical intermediate complexes of the Reformatsky reaction for the synthesis of β-hydroxy acids are also obtainable from furfural.[13] Like benzaldehyde, furfural adds chloroform under the influence of alkali with formation in the latter instance, of (trichloromethyl)furylcarbinol, I, b.p. 115–118° (120 mm.); d_{20}^{20} 1.452; n_D^{25} 1.5346.[14]

$$C_4H_3O\text{—}CHO + CHCl_3 \xrightarrow{KOH} C_4H_3O\text{—}CH(OH)\text{—}CCl_3$$

I

Furfural has a rather high order of stability toward heat in the absence of catalytic materials and oxygen.[15, 16] Hurd[17] found the initial decomposition temperature to be 565° for a contact time of twenty seconds. The products are carbon monoxide and furan, and pyrolysis products of the latter. In the presence of suitable catalysts, decarbonylation takes place at considerably lower temperatures, and this is the basis of the commercial procedure for the production of furan (Chapter 2). For the action of electric discharge on furfural in an atmosphere of nitrogen, see Berthelot.[18]

Like other aldehydes, furfural condenses with suitably activated $>CH_2$ groups, as in the well-known Perkin and Claisen reactions for preparing

[4] Marini-Bettolo and Paolini, *Gazz. chim. ital.*, **75**, 78 (1945); *C. A.*, **41**, 3444 (1947).
[5] Baroni and Marini-Bettolo, *Gazz. chim. ital.*, **70**, 670 (1940); *C. A.*, **35**, 5106 (1941).
[6] Gentilini, *Ann. staz. sper. viticolt. enol. Conegliano*, **11**, 243 (1942–1943); *C. A.*, **40**, 3218 (1946).
[7] Marini-Bettolo and Baroni, *Ricerca sci. e ricostruz.*, **17**, 435 (1947); *C. A.*, **43**, 7000 (1949).
[8] Ahrens and Stapler, *Ber.*, **38**, 3259 (1905).
[9] Duprat, *Bull. inst. pin.*, **1933**, 17, 36; *C. A.*, **27**, 2674 (1933).
[10] Wagener and Tollens, *Ber.*, **39**, 410 (1906).
[11] Adams and Vollweiler, *J. Am. Chem. Soc.*, **40**, 1732 (1918).
[12] Pawlinoff and Wagner, *Ber.*, **17**, 1967 (1884).
[13] English and Gregory, *J. Am. Chem. Soc.*, **69**, 2123 (1947).
[14] Howard, *J. Am. Chem. Soc.*, **47**, 455 (1925).
[15] Dunlop and Peters, *Ind. Eng. Chem.*, **32**, 1639 (1940).
[16] Dunlop, *Ind. Eng. Chem.*, **40**, 204 (1948).
[17] Hurd, Goldsby and Osborne, *J. Am. Chem. Soc.*, **54**, 2532 (1932).
[18] Berthelot, *Compt. rend.*, **126**, 671 (1898).

α,β-unsaturated acids and esters, the Knoevenagel reaction, and aldol-type condensations. While most of the reactions of this type are discussed elsewhere under the appropriate type of product, it seems advisable to illustrate several at this point.

Reaction of furfural with aliphatic aldehydes and ketones under the influence of a basic condensing agent generally proceeds, with loss of water, to give furylalkenals and furylalkenones, respectively; with acetaldehyde, furylacrolein (p. 415) is produced. The intermediate aldols have not been described, although it has been reported that careful control of temperature and pH during the condensation reaction permits their isolation, at least in crude form. Thus, Schmauss and Haberland[19] treated furfural with acetaldehyde at 0–10° and at a pH of 10–11, and obtained the aldol, II, which was reduced directly to 1-furyl-1,3-propanediol, III. Similarly, Lindauer[20] obtained 2,2-dimethyl-3-(2-furyl)-1,3-propanediol by reduction of the aldol formed when a mixture of furfural and isobutyraldehyde was shaken in the cold with saturated, aqueous potash.

$$C_4H_3O\text{—}CHO + CH_3CHO \xrightarrow{KOH} \underset{II}{C_4H_3O\text{—}CH(OH)CH_2CHO} \xrightarrow{Na\text{—}Hg} \underset{III}{C_4H_3O\text{—}CH(OH)CH_2CH_2OH}$$

1-Furyl-1,3-propanediol: III; b.p. 141-142° (9 mm.).[19]

2,2-Dimethyl-3-(2-furyl)-1,3-propanediol: $C_4H_3O\text{—}CH(OH)C(CH_3)_2CH_2OH$; m.p. 63–64°; b.p. 257° (atm.); **diacetate,** b.p. 176-177° (42 mm.).[20]

1-Furyl-1,3-butanediol: $C_4H_3O\text{—}CH(OH)CH_2CH(OH)CH_3$; b.p. 139–140° (7 mm.); 145–146° (12 mm.); by reduction of the aldol derived from furfural and acetone.[19, 21]

1-Furyl-2-methyl-1,3-butanediol (?): $C_4H_3O\text{—}CH(OH)CH(CH_3)CH(OH)CH_3$; b.p. 147-148° (12 mm.); by reduction of the aldol obtained by interaction of furfural and methyl ethyl ketone in aqueous, alkaline medium.[21] In view of the discussion presented elsewhere (p. 454) on the subject of the latter reaction, it seems likely that the reduction product is actually the isomeric 1-furyl-1,3-pentanediol.

1-Furyl-3-phenyl-1,3-propanediol: $C_4H_3O\text{—}CH(OH)CH_2CH(OH)\text{—}C_6H_5$. What may have been the **diacetate** (m.p. 149°) of the diol was obtained by reduction of benzoylfuroylmethane (p. 440) with sodium amalgam in acetic acid.[22]

1,6-Difuryl-2,2,5,5-tetraphenyl-1,6-hexanediol: $[C_4H_3O\text{—}CH(OH)C\text{—}(C_6H_5)_2CH_2]_2$; m.p. 212–213°. This product deposited when the condensation product of furfural and disodium-tetraphenylbutane was allowed to stand over water.[23]

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[19] Schmauss and Haberland, "Furfural Condensation," PB. No. **739**, U. S. Dept. Commerce, 1943.

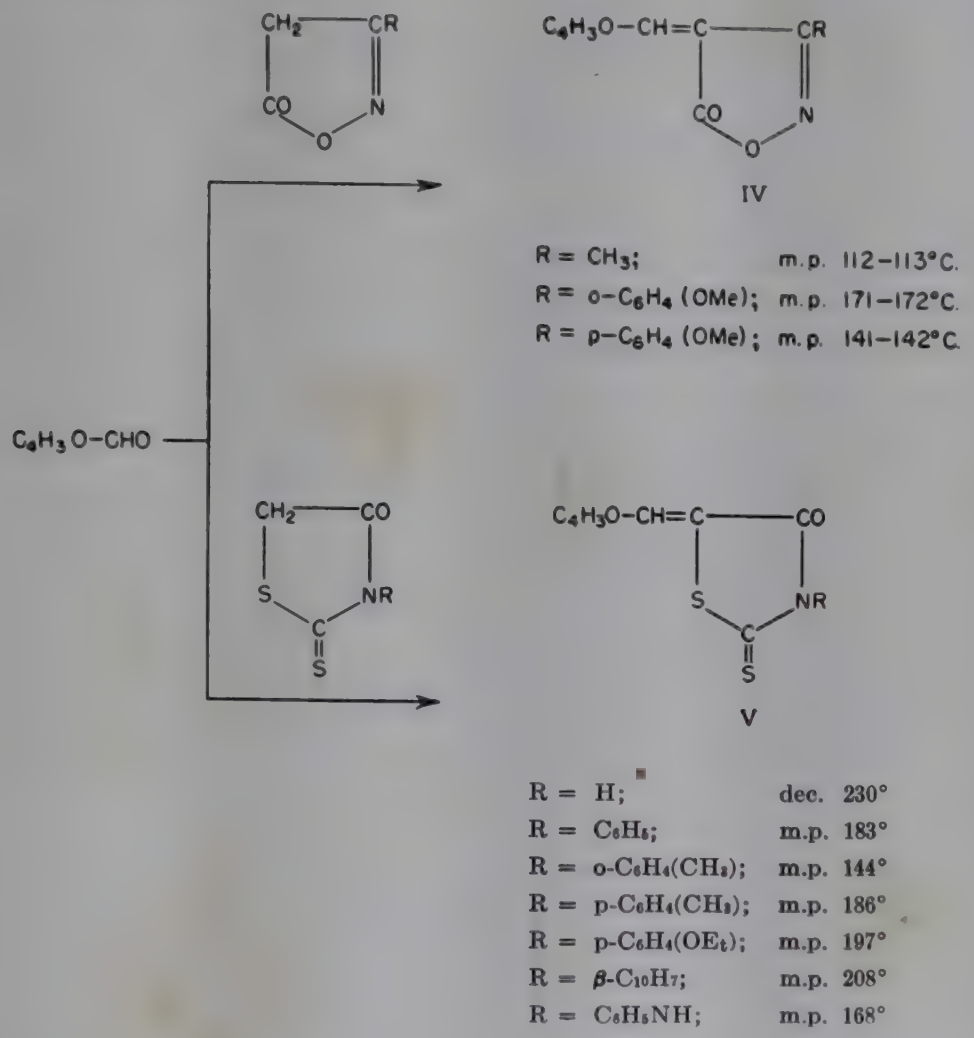
[20] Lindauer, *Monatsh.*, **21**, 72 (1900).

[21] Haberland and Himmen (to I. G. Farbenindustrie Akt.-Ges.), German Pat. 702,894 (1941); *C. A.*, **36**, 779 (1942).

[22] Semmler and Ascher, *Ber.*, **42**, 2355 (1909).

[23] Schlenk and Bergmann, *Ann.*, **463**, 1 (1928).

The formation of furfurylideneisoxazolones, IV,[24, 25] and furfurylidene-rhodaninic acids (5-furfurylidene-4-thiazolone-2-thione), V[26, 27, 28, 29, 30], is accomplished by condensation of the aldehyde with the indicated compounds as illustrated below. Nitriles possessing an adjacent methylene



group likewise condense with elimination of the elements of water to give derivatives of acrylonitrile, C_4H_3O—CH=CRCN (p. 622). Thus, Legrand[31] synthesized furfurylideneglutaconononitrile, C_4H_3O—CH=C(CN)-CH=CHCN, m.p. 141–141.5°, by heating furfural with glutaconononitrile in the presence of a small quantity of piperidine. Similarly, Langkammerer[32]

[24] Wahl and Silberzweig, *Bull. soc. chim.* (4), **13**, 236 (1913).
[25] Schiff and Betti, *Ber.*, **30**, 1337 (1897).
[26] Andreasch and Zipser, *Monatsh.*, **26**, 1191 (1905).
[27] Andreasch, *Monatsh.*, **27**, 1211 (1906).
[28] Stuchetz, *Monatsh.*, **26**, 1209 (1905).
[29] Wagner, *Monatsh.*, **27**, 1233 (1906).
[30] Bargellini, *Gazz. chim. ital.*, **36, II**, 129 (1906).
[31] Legrand, *Bull. soc. chim. Belg.*, **53**, 166 (1944); *C. A.*, **40**, 4671 (1946).
[32] Langkammerer (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,462,107 (1949); *C. A.*, **43**, 3847 (1949).

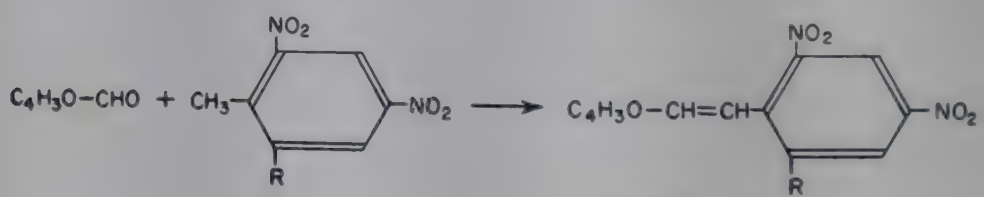
describes the production of 1,6-difuryl-2,5-dicyano-1,3,5-hexatriene, VI, m.p. 225–227°, by reaction of 1,4-dicyano-2-butene with two molecular equivalents of furfural under the influence of sodium ethoxide. The product, VI, is reported to be useful as a dye, or as an intermediate in the preparation of polyamide resins.

$$2\,C_4H_3O{-}CHO + CH_2(CN){-}CH{=}CH{-}CH_2CN \xrightarrow{NaOEt}$$

$$C_4H_3O{-}CH{=}C(CN)CH{=}CHC(CN){=}CH{-}C_4H_3O$$

VI

With the nitroparaffins, ω-nitrovinylfurans, $C_4H_3O{-}CH{=}CRNO_2$, (p. 167) are obtained, although Kanao[33] has shown that experimental conditions can be chosen to permit isolation of the intermediate α-nitro alcohols, $C_4H_3O{-}CH(OH)CH(NO_2)R$ (p. 219). Furfural also condenses with appropriate aromatic nitro compounds, as for example, with 2-nitrofluorene to give the 9-furfurylidene derivative, m.p. 213.5–214.5°[34]; with 4,6-dinitro-1,3-xylene to produce mono- (m.p. 138°) and difurfurylidene (m.p. 235°) derivatives.[35] Similarly, 2,4-dinitro- and 2,4,6-trinitrotoluene have been condensed with furfural in the presence of a small amount of piperidine to obtain the expected styrene derivatives, VII.[36, 37, 38] For reduction of VII (R = H) to 2-(nitroaminostyryl)furan (two isomers, m.p. 86–88° and 103.5–131.5°, respectively), see Simpson.[39] The related 2-(*p*-



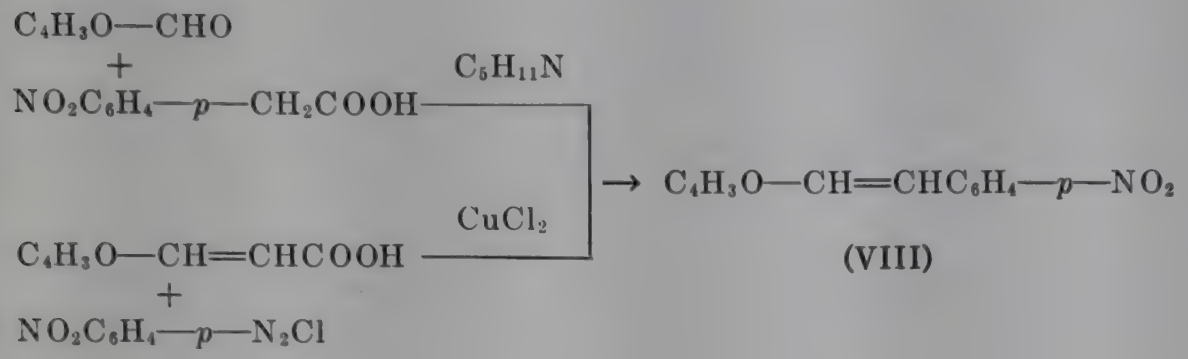
(VII)

R = H; m.p. 135°-135.5°
R = NO_2; m.p. 123°-124°,128°

nitrostyryl)furan and the *o*-nitro isomer are also known, although not obtained directly from furfural and nitrotoluene. The former, VIII (m.p. 130–131°), was synthesized[40, 41, 41a] by two separate routes as indicated

[33] Kanao, *J. Pharm. Soc. Japan*, **550**, 1019 (1927); *C. A.*, **22**, 1588 (1928).
[34] Loevenich and Loeser, *J. prakt. Chem.*, **116**, 325 (1927).
[35] Ruggli, Zimmermann and Thouvay, *Helv. Chim. Acta*, **14**, 1250 (1931).
[36] Kasiwagi, *Bull. Chem. Soc. Japan*, **2**, 110 (1927); *C. A.*, **21**, 2895 (1927).
[37] Pastak, *Bull. soc. chim.*, **39**, 72 (1926).
[38] Parkes and Farthing, *J. Chem. Soc.*, **1948**, 1275.
[39] Simpson, *J. Chem. Soc.*, **1943**, 447.
[40] Brown and Kon, *J. Chem. Soc.*, **1948**, 2147.
[41] L'Ecuyer and Olivier, *Can. J. Research*, **27**, B, 689 (1949).
[41a] Cordier and Cagniant, *Compt. rend.*, **228**, 1950 (1950).

below. The latter[42] was isolated in both *cis* (b.p. 152–154° (3 mm.)) and *trans* (m.p. 92.8–93.6°) forms by decarboxylation of the corresponding isomeric forms of α-(2-furyl)-*o*-nitrocinnamic acid (see p. 588).



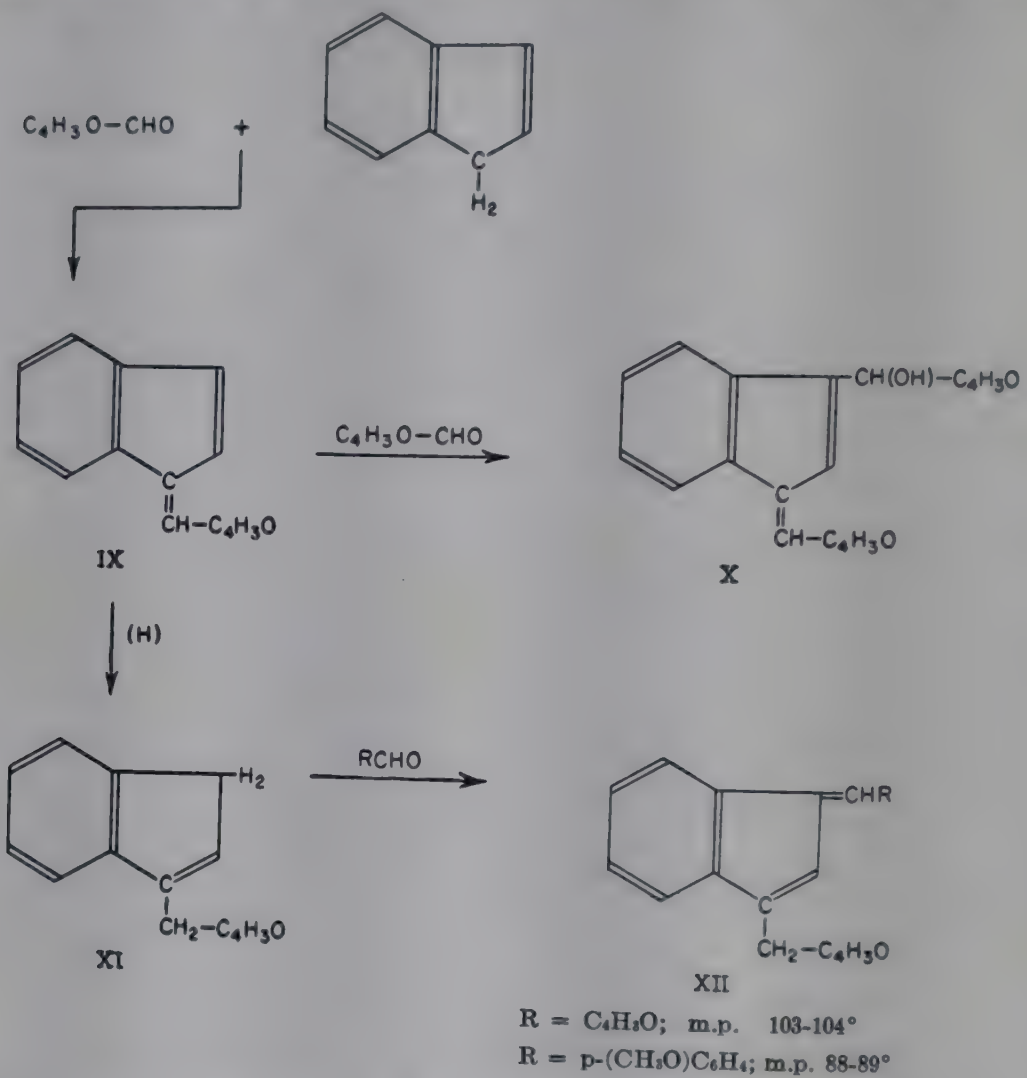
(VIII)

Furfurylidine-γ-picoline, $C_4H_3O—CH=CH—C_5H_4N$ (picrate, m.p. 212–214°; methiodide, m.p. 202–203°) has been prepared in the conventional manner.[43, 44] The isomeric α-picoline derivative, m.p. 51–53°, was obtained by heating furfural and α-picoline in the presence of zinc chloride[45]; the related furfurylidenequinaldine (no constants) was similarly prepared from the aldehyde and quinaldine.[46] In the absence of a condensing agent, aqueous α-picoline is reported to combine directly with furfural without loss of water to form $C_4H_3O—CH(OH)CH_2—C_5H_4N$ [b.p. 164° (20 mm.); m.p. 41–43°; benzoate, m.p. 47–49°].[47] When furfural is heated with ethyl 4-methylnicotinate at 160° for 20 hours the furfurylidene derivative, m.p. 67.5–68° is obtained which gives a picrate, m.p. 179–181°.[48]

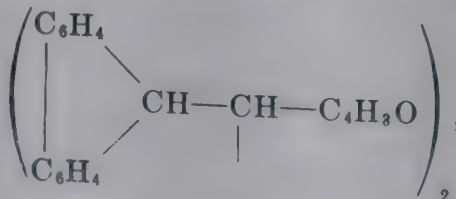
Nothing has been reported on the condensation of furfural with cyclopentadiene under alkaline conditions. However, the related indene gives rise to 1-furfurylideneindene (furylbenzofulvene), IX, m.p. 86–86.5°; 3-methylindene, to the homologous fulvene, m.p. 77–77.5°.[49] With two molecular proportions of the aldehyde, indene is converted into a yellow crystalline product, m.p. 114.5–115°, which Wuest[49] has formulated as furyl-3-(1-furfurylideneindenyl)carbinol, X. Reduction with aluminum amalgam converts IX into 3-furfurylindene, XI, b.p. 166–168° (15 mm.)

[42] Amstutz and Spitzmiller, *J. Am. Chem. Soc.*, **65**, 367 (1943).
[43] Gilman and Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).
[44] Phillips, *J. Org. Chem.*, **14**, 302 (1949).
[45] Merck, *Ber.*, **21**, 2709 (1888).
[46] Srpek, *Ber.*, **20**, 2044 (1887).
[47] Klein, *Ber.*, **23**, 2693 (1890).
[48] Beer and Preobrazhenskii, *J. Gen. Chem. U.S.S.R.*, **16**, 858 (1946); *C. A.*, **41**, 122 (1947).
[49] Wuest, *Ann.*, **415**, 291 (1918).

which may be condensed with aldehydes to obtain the indicated benzofulvenes, XII.[49] In the same way, furfural and fluorene condense under the



influence of sodium ethoxide to give furfurylidenefluorene[50]; reduced to furfurylfluorene, m.p. 91–92°[51] and to 1,2-difuryl-1,2-di(9-fluorenyl)ethane

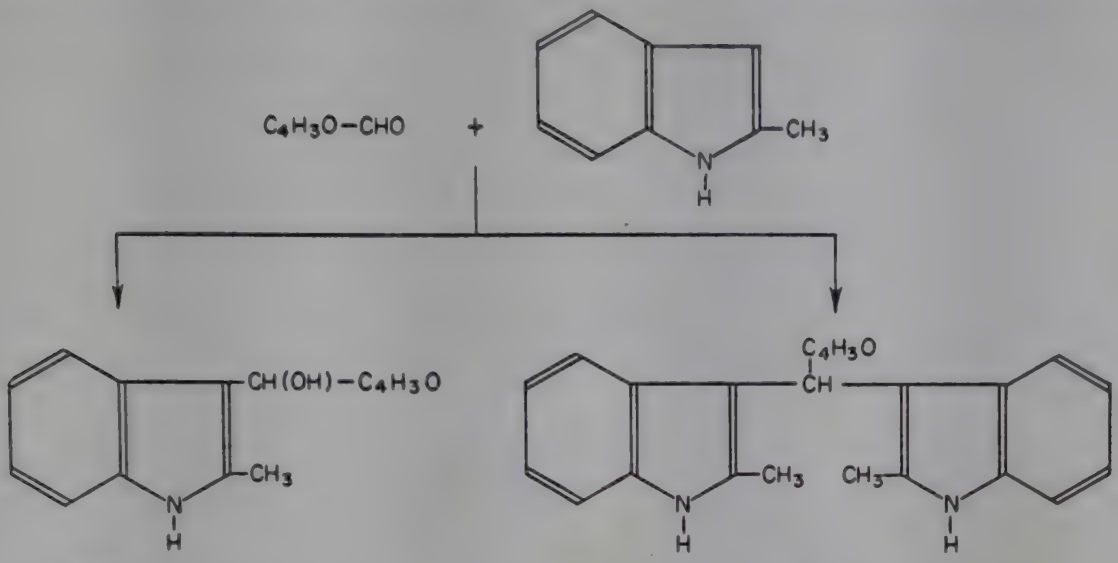


, m.p. 238–242°[23].

2-Methylindole also condenses with furfural. Thus, Scholtz[52] reports the formation of the methyl (m.p. 108°) and ethyl (m.p. 158°) ethers of furyl-(2-methyl-3-indolyl)carbinol, XIII, when the reactants are brought together in methanol and ethanol, respectively, in the presence of sodium hydroxide. However, when two moles of 2-methylindole and one of the aldehyde are heated at 100° for several hours, the product is 3-furfuryl-

[50] Wawzonek and Fan, *J. Am. Chem. Soc.*, **68**, 2541 (1946).
[51] Thiele and Heule, *Ann.*, **347**, 290 (1906).
[52] Scholtz, *Ber.*, **46**, 2138 (1913).

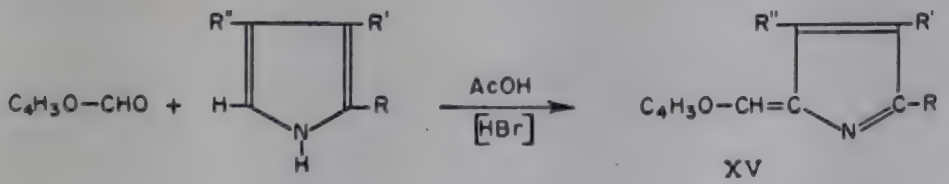
idenebis-2-methylindole, XIV, m.p. 220°.[53] Related to the latter is furfurylidenebispyrrocoline, $C_4H_3O—CH(C_8H_6N)_2$, m.p. 148–149°, derived by reaction of furfural with pyrrocoline.[54] Scholtz[55] also prepared furfurylidene



XIII XIV

derivatives of methylpicolide and methylpyrindole. Furfurylidene-5,7- dimethyloxindole, m.p. 246°.[56]

The reaction of furfural with pyrrole compounds having a free α-position was studied by Piutti.[57] In the presence of mineral acid, he reports the formation of products related to the dipyrrylmethenes (see XV, below). Tetrahydroscatole condensed similarly under the influence of picric acid, giving rise to $N{=}C{-}CH_2CH_2CH_2CH_2{-}C{=}CMe{-}C{=}CH{-}C_4H_3O$, as the picrate which decomposes without fusion up to 280°.[57] On the other hand, by merely heating the aldehyde with 2-(1,3-butadienyl)-pyrrole, Scholtz[54] obtained 5-furfurylidenebis-2-(1,3-butadienyl)pyrrole,



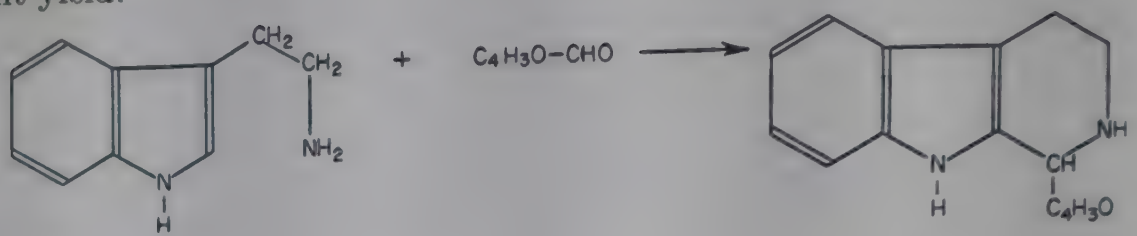
XV

R	R'	R''	Physical constants
CH_3	C_2H_5	CH_3	m.p. 185°; picrate, m.p. 154°
CH_3	CH_3CO	CH_3	perchlorate, dec. 280°

$C_4H_3O—CH(C_4H_3N—CH{=}CHCH{=}CH_2)_2$, m.p. 132°. Somewhat related to these reactions is the condensation of furfural with tryptamine

[53] Renz and Loew, *Ber.*, **36**, 4326 (1903).
[54] Scholtz, *Ber.*, **45**, 734 (1912).
[55] Scholtz, *Arch. Pharm.*, **251**, 666 (1913); **253**, 629 (1915).
[56] Livovschi, *Compt. rend.*, **203**, 1265 (1936).
[57] Piutti, *Gazz. chim. ital.*, **66**, 265 (1936); *C. A.*, **31**, 1398 (1937).

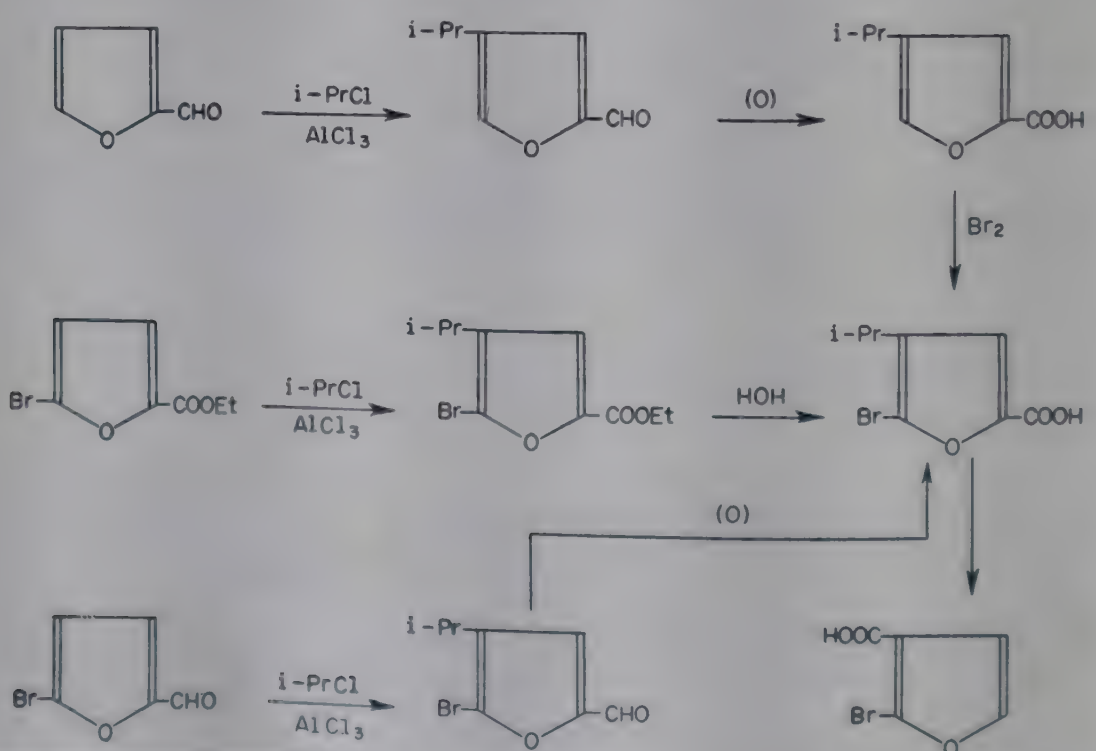
hydrochloride which gives rise to XVI, m.p. 122° (unstable) in 10 per cent yield.[58]



XVI

The reaction of furfural with phenolic compounds is discussed elsewhere (p. 399). For the condensation of furfural with various bile constituents, such as dehydrocholic and dehydrodesoxycholic acids, see Kaziro.[59, 60]

For the most part, the nuclear substitution reactions of furfural are dealt with under the appropriately substituted furan compounds. However, alkylation by the Friedel-Crafts procedure merits special mention. In the furan series, incoming groups or atoms are directed to an α-position of the nucleus if such a position is available, and furfural behaves in accordance with this generalization in all but one reported instance. The exception is concerned with the alkylation of furfural with isopropyl chloride and aluminum chloride which gives rise to 4-isopropylfurfural, a most unexpected orientation. The structure of the product was proven rigorously by these reaction sequences:[61, 62, 63]



[58] Hahn, Bärwald, Scales and Werner, *Ann.*, **520**, 107 (1935).
[59] Kaziro, *J. Biochem. Japan*, **7**, 283 (1927); *C. A.*, **22**, 602 (1928).
[60] Kaziro, *Z. physiol. Chem.*, **185**, 151 (1929); *C. A.*, **24**, 859 (1930).
[61] Gilman, Calloway and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).

The possibility that the isopropyl group had initially entered the 5-position and then underwent rearrangement to the 4-position was negated when it was demonstrated[64] that 5-isopropylfurfural, prepared from the corresponding acid, was stable to aluminum chloride under the conditions of the alkylation experiment. The anomalous orientation is the more peculiar when it is considered that alkylation of furfural with butyl and pentyl chlorides introduces an alkyl substituent at the 5-position. In these reactions with the higher alkyl chlorides, however, there was observed a peculiarity similar to that experienced in connection with the alkylation of 2-furoic ester (p. 499). That is, irrespective of whether *n*-, *i*-, or *t*-butyl halide was employed, the isolated product was reported to be 5-*t*-butylfurfural although in every experiment the yield leaves much to be desired.[64] Similarly, alkylation of furfural with *n*-pentyl chloride and aluminum chloride[64] was held to produce 5-*t*-pentylfurfural since oxidation yielded a 5-pentyl-2-furoic acid[63] the properties of which checked closely with the acid obtained by Reichstein[65] following alkylation of methyl 2-furoate with *t*-pentyl chloride. For the properties of the alkylfurfurals, the reader is referred to p. 403. For the action of furfural on toluene in the presence of aluminum chloride, see Hey.[66]

For the attempted sulfonation of furfural, see Terent'ev.[67, 68]

Functional Derivatives

Acetals and Acylals

Furfural ethyl acetal has been prepared in high yield by condensation of furfural with orthoformic ester under the influence of ammonium chloride[69] (see also [70, 71, 72]) and by reaction of the same reagent with 2-furylmagnesium iodide.[73] It has also been obtained by the less costly procedure involving reaction of furfural with alcohol using a catalytic quantity of hydrogen chloride, although a large excess of alcohol is required in order to attain a reasonable conversion of the furfural. A kinetic study of

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[62] Gilman, McCorkle and Calloway, *J. Am. Chem. Soc.*, **56**, 745 (1934).
[63] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[64] Gilman and Burtner, *J. Am. Chem. Soc.*, **57**, 909 (1935).
[65] Reichstein, Rosenberg and Eberhardt, *Helv. Chim. Acta*, **18**, 721 (1935).
[66] Hey, *J. Chem. Soc.*, **1935**, 72.
[67] Terent'ev, *Vestnik Moskov. Univ.*, **1947**, 9; *C. A.*, **44**, 1480 (1950).
[68] Terent'ev and Kazitsyna, *Zhur. Obshchei Khim. J. Gen. Chem.*, **19**, 531 (1949); *C. A.*, **43**, 7015 (1949).
[69] Claisen, *Ber.*, **40**, 3903 (1907).
[70] Claisen, *Ber.*, **31**, 1010 (1898).
[71] Scheibler, Sotscheck and Friese, *Ber.*, **57**, 1443 (1924).
[72] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany, 1930.
[73] Gilman and Franz, *Rec. trav. chim.*, **51**, 991 (1932).

this reaction was included in the extensive work of Adkins and his coworkers[74, 75, 76, 77] on the effect of structure of reactants on the extent of acetal formation by this general method. Their findings show that furfural and other α,β-unsaturated aldehydes (benzaldehyde, acrolein, crotonaldehyde, etc.) react with various monohydric alcohols at a greatly enhanced rate, but considerably less completely, compared to saturated aldehydes (tetrahydrofurfural and acetaldehyde). Thus, while furfural reacts several hundred times as rapidly as tetrahydrofurfural under the same conditions, the concentration of acetal at equilibrium is less than one-half of that in the latter instance.

TABLE 1. EXTENT OF ACETAL FORMATION WITH VARIOUS ALCOHOLS[77]

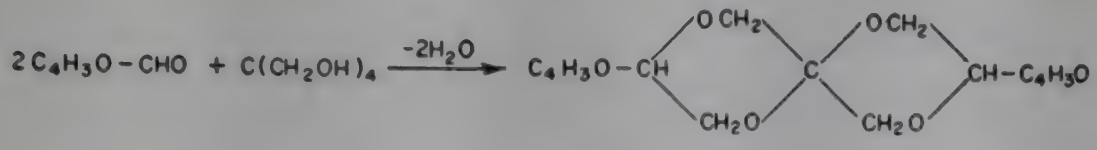
$$C_4H_3O\text{—}CHO + 2\ ROH \underset{}{\overset{HCl}{\rightleftharpoons}} C_4H_3O\text{—}CH(OR)_2 + H_2O$$

Alcohol	Molar ratio (alcohol/furfural)	Conversion (%)	K_e (25°)
Heptyl	5	68	0.58
Methyl	5	42	0.100
Methyl	11	61	0.114
Ethyl[76]	2.0	17	0.036
Ethyl	6.1	44	0.036
Ethyl	6.2	33	0.035
Ethyl	9.8	40	0.034
Ethyl	11.1	44	0.039
Isopropyl	11	25	0.009
1-Methylheptyl	5	11	0.003
t-Butyl	6	0	0.000

With 1,2- and 1,3-dihydroxy compounds, furfural condenses to form cyclic acetals. Excellent yields of these types have been obtained by carrying out the reaction, with or without a catalyst (H_2SO_4, $CH_3C_6H_4SO_3H$-*p*, H_3PO_4, $CaCl_2$, etc.), so that the formed water is continuously removed as by azeotropic distillation with benzene, toluene or other suitable entraining agent. This procedure was first suggested by Hoover[78] and was later employed by Salmi and Jansson[79, 80] and by Hinz.[81] The spirocyclic acetal, I, is produced by heating furfural with pentaerythritol in the presence of

[74] Adams and Adkins, *J. Am. Chem. Soc.*, **47**, 1358 (1925).
[75] Adkins and Adams, *J. Am. Chem. Soc.*, **47**, 1368 (1925).
[76] Adkins, Semb and Bolander, *J. Am. Chem. Soc.*, **53**, 1853 (1931).
[77] Minné and Adkins, *J. Am. Chem. Soc.*, **55**, 299 (1933).
[78] Hoover (to Association of American Soap and Glycerine Producers), U. S. Pat. 1,934,309 (1934); *C. A.*, **28**, 485 (1934).
[79] Salmi, *Ber.*, **71**, 1803 (1938).
[80] Salmi and Jansson, *Suomen Kemistilehti*, **12**, B, 28 (1939); *C. A.*, **34**, 423 (1940).
[81] Hinz, Meyer and Schücking, *Ber.*, **76**, 676 (1943).

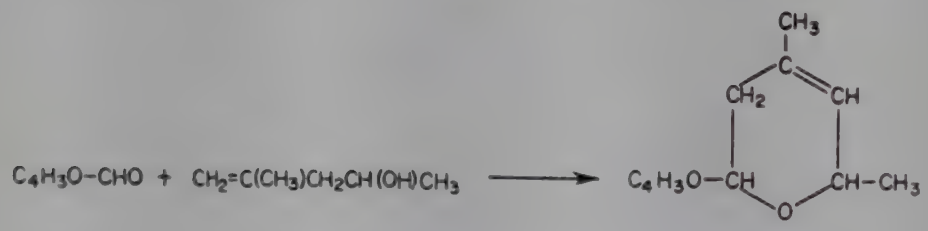
sulfuric acid[82] or zinc chloride.[83] The corresponding mercaptal is also known (p. 378). For cyclic acetals derived from nitroalkanediols, see Senkus.[84]



I

The acid-catalyzed condensations of mannitol or sorbitol with excess furfural give rise to a mixture of mono- and trifurfurylidene derivatives. Partial hydrolysis converts trifurfurylidenesorbitol into difurfurylidenesorbitol, whereas attempts to effect a similar transformation with trifurfurylidenemannitol were unsuccessful.[85]

With the unsaturated alcohol, 4-methyl-4-penten-2-ol (II), condensation with furfural in the presence of an acidic catalyst gives rise to 6-furyl-2,4-dimethyl-5,6-dihydro-2*H*-pyran, III, b.p. 83.8–84.4° (5 mm.).[86]

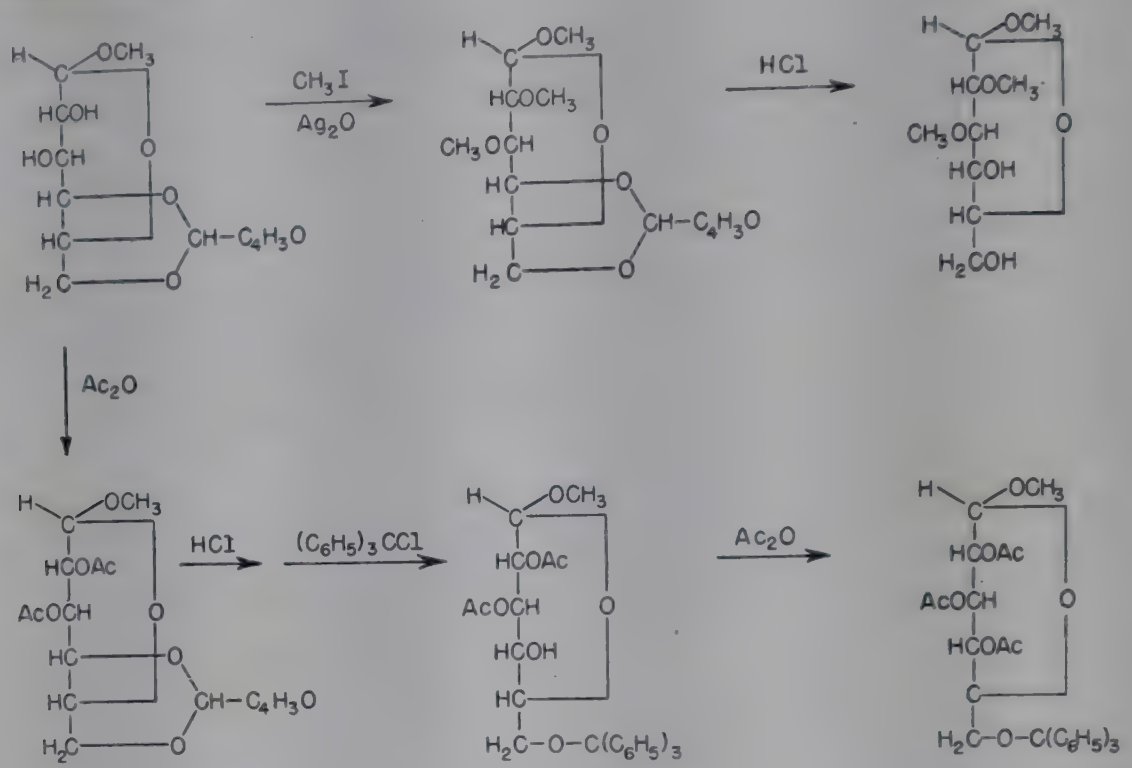


II III

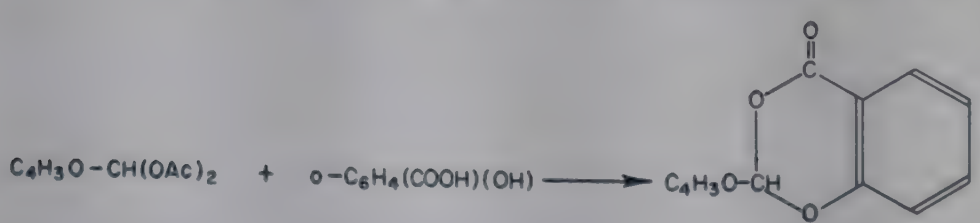
Bredereck[87, 88, 85] studied the reaction of furfural with glucose and with derivatives of this and other hexoses. In the first instance he isolated a syrupy condensation product which, on subsequent acetylation, produced 4,6-furfurylidene-2,3-diacetyl-β-D-glucosyl acetate. Methyl α- and β-D-glucosides, methyl α-D-galactoside, and methyl α-D-mannoside likewise give rise to the corresponding 4,6-furfurylidene derivatives, but the configuration of the mannoside also permits formation of the 2,3-4,6-difurfurylidene compound. The configuration of these cyclic acetals was ascertained by methylation or acetylation and splitting off the furfurylidene radical to obtain sugar derivatives of known constitution. The reactions

[82] Read, *J. Chem. Soc.*, **101**, 2090 (1912); *Proc. Chem. Soc.*, **28**, 240 (1912).
[83] Backer and Schurink, *Rec. trav. chim.*, **50**, 1066 (1931).
[84] Senkus (to Commercial Solvents Corp.), U. S. Pat. 2,297,921 (1942); *C. A.*, **37**, 1448 (1943).
[85] Bredereck and Papademetriu, *Ber.*, **70**, 797 (1937).
[86] Williams and Ballard (to Shell Development Co.), U. S. Pat. 2,452,977 (1948); *C. A.* **43**, 3042 (1949).
[87] Bredereck, *Ber.*, **68**, 777 (1935).
[88] Bredereck, *Ber.*, **68**, 2299 (1935).

are illustrated below for the particular case of methyl 4,6-furfurylidene-α-D-glucoside.



Furfural diacetate: m.p. 52–53°; b.p. 143–144° (20 mm.). This, the only reported furfural acylal, is best prepared by reacting furfural with acetic anhydride in the cold, using stannous chloride as the condensing agent[91] (see also [92, 93, 94, 95, 96, 71]). For a kinetic study of vapor-phase decomposition of the diacetate, see Dacey and Coffin.[97] Condensation with salicylic acid under the influence of sulfuric acid produces resins for the most part, but it is possible to isolate a small amount of 2-furyl-4-oxo-1,3-benzodioxane, IV, m.p. 90°.[98] For the action of perbenzoic acid on furfural



IV

[89] Neish and Macdonald, *Can. J. Research*, **25, B,** 70 (1947).
[90] Wolfen-Farben, "Softening Agents and Solvents from Furfural," PB No. **42456,** U. S. Dept. Commerce, 1940.
[91] Gilman and Wright, *Rec. trav. chim.*, **50,** 833 (1931).
[92] Gilman and Wright, *Iowa State Coll. J. Sci.*, **4,** 35 (1929).
[93] Burdick and Adkins, *J. Am. Chem. Soc.*, **56,** 438 (1934).
[94] Law, *Chem. Ztg.*, **32,** 366 (1908).
[95] Blanksma, *Chem. Weekblad*, **6,** 717 (1909); *C. A.*, **4,** 752 (1910).
[96] Knoevenagel, *Ann.*, **402,** 111 (1914).
[97] Dacey and Coffin, *Can. J. Research*, **15, B,** 260 (1937).
[98] Mowry, *J. Am. Chem. Soc.*, **69,** 2362 (1947).

Table 2. Furfural Acetals

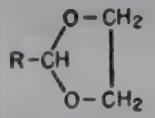
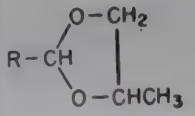
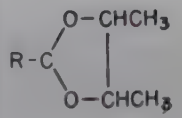
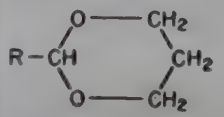
Product	Structure (R = 2-C_4H_3O)	Physical constants	Ref.
From monohydric alcohols			
Furfurylidenedimethyl acetal	R—CH$(OCH_3)_2$	b.p. 178 (—)	74
Furfurylidenediethyl acetal	R—CH$(OC_2H_5)_2$	b.p. 77–79 (16 mm.), 184–185 (740 mm.) d_{20}^{20} 0.9994; n_D^{20} 1.44506	76, 71, 69, 72
Furfurylidenedi-*i*-propyl acetal	R—CH$(O\text{-}i\text{-}C_3H_7)_2$	b.p. 201 (—)	74
Furfurylidenebis-β-ethoxyethyl acetal	R—CH$(OCH_2CH_2OC_2H_5)_2$	b.p. 131–132 (2 mm.), 259 (740 mm.) n_D 1.4534; d_4^{25} 1.0374	77
From dihydric alcohols			
Furfurylidene ethylene acetal		b.p. 91–93 (16 mm.), n_D^{20} 1.4854; d_4^{20} 1.1941	79, 80, 78, 81
Furfurylidene propylene acetal		b.p. 97–99 (19–21 mm.) n_D^{20} 1.4767; d_4^{20} 1.1414	79, 80
Furfurylidene α,β-dimethylethylene acetal		b.p. 206 (760 mm.) n_D^{20} 1.4645; d_4^{15} 1.0770 $[\alpha]_D^{25} = -26.6$	89
Furfurylidene trimethylene acetal		b.p. 114.8–116.5 (16 mm.) n_D^{20} 1.4919; d_4^{20} 1.1678	79, 80

TABLE 2—*Continued*

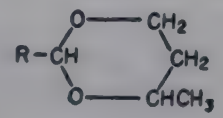
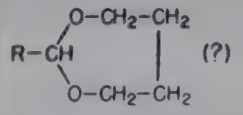
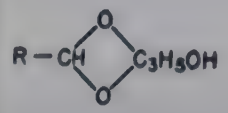
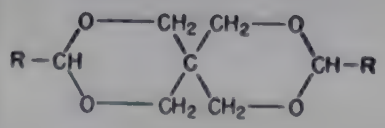
Product	Structure (R = 2-C_4H_3O)	Physical constants	Ref.
Furfurylidene α-methyltrimethylene acetal		b.p. 121.5–122.5 (18–20 mm.) n_D^{20} 1.4846; d_4^{20} 1.1188	79, 80
Furfurylidene tetramethylene acetal	 (?)	b.p. 112 (13 mm.)	81
Furfurylidenebis-4-hydroxybutyl acetal	$R—CH(OCH_2CH_2CH_2CH_2OH)_2$	b.p. 103 (4 mm.)	81
From polyhydric alcohols			
Furfurylideneglycerol		b.p. 154–156 (14 mm.), 267–268 (atm.) (dec.) d^{20} 1.273 **acetate,** b.p. 146–150 (7 mm.)	78, 90
Difurfurylidenepentaerythritol		m.p. 161, 164–165	82, 83
2,4(?)-Furfurylidenesorbitol		m.p. 192–193	85
2,4–5,6(?)-Difurfurylidenesorbitol		m.p. 202–203	85
1,3-2,4-5,6(?)-Trifurfurylidenesorbitol		m.p. 186–187 $[\alpha]_D^{23} = +19.7$ ($CHCl_3$)	85

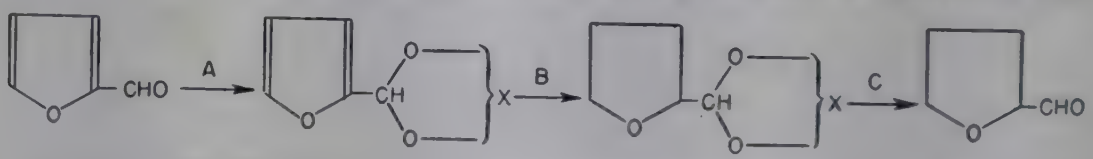
TABLE 2—*Continued*

Product		Physical constants	Ref.
Furfurylidenemannitol		m.p. 126 $[\alpha]_D^{21} = +19.0$ (H_2O)	85
Trifurfurylidenemannitol		m.p. 176 $[\alpha]_D^{16} = -32.3$ ($CHCl_3$)	85
4,6-Furfurylidene-β-D-glucose		syrup **1,2,3-triacetyl deriv.**, m.p. 203–204; $[\alpha]_D^{25} = -46.6$ ($CHCl_3$)	88
Methyl 4,6-furfurylidene-α-D-glucoside		m.p. 153–154 $[\alpha]_D^{25} = +84.4$ (H_2O) **2,3-diacetyl deriv.**, m.p. 112–113 **2,3-dimethyl deriv.**, m.p. 119–120; $[\alpha]_D^{25} = +98.4$ ($CHCl_3$)	87
Methyl 4,6-furfurylidene-β-D-glucoside		m.p. 160–162 $[\alpha]_D^{24} = -97.2$ (C_5H_5N) **2,3-diacetyl deriv.**, m.p. 205–207; $[\alpha]_D^{24} = -85.1$ ($CHCl_3$)	88
Methyl 4,6-furfurylidene-α-D-galactoside		m.p. 160–161 $[\alpha]_D^{20} = +157.6$ (H_2O) **2,3-diacetyl deriv.**, m.p. 125–126 **2,3-dimethyl deriv.**, m.p. 138–140; $[\alpha]_D^{20} = +127.9$ ($CHCl_3$)	85
Methyl 4,6-furfurylidene-α-D-mannoside		m.p. 153–154 $[\alpha]_D^{25} = +64.5$ ($CHCl_3$) **2,3-diacetyl deriv.**, m.p. 142–143 $[\alpha]_D^{25} = +32.9$ (H_2O)	87
Methyl 2,3-4,6-difurfurylidene-α-D-mannoside		m.p. 182–184 $[\alpha]_D^{25} = +42.45$ ($CHCl_3$)	87

diacetate, see Scheibler.[99] Furfural diacetate undergoes the Diels-Alder reaction with maleic anhydride to give an adduct, m.p. 126.5–127°.[100]

A number of attempts have been made to employ several of the acetals and also furfural diacetate as intermediates for the synthesis of tetrahydrofurfural. Thus, it is possible, under selected conditions[101] to reduce these types catalytically with hydrogen with comparatively little attack on the side chain. In this way, tetrahydrofurfural ethyl and ethylene acetals, and tetrahydrofurfural diacetate have been prepared in relatively good yield. However, hydrolysis to the free aldehyde and isolation of the latter is rendered difficult due to instability in acidic, aqueous medium; and the over-all yield of tetrahydrofurfural based on furfural is uniformly low as indicated in Table 3. Probably the best method for synthesizing the saturated aldehyde is that involving oxidation of tetrahydrofurfuryl alcohol over a silver oxide catalyst, as recently reported by Bremner.[102]

TABLE 3. YIELD OF TETRAHYDROFURFURAL FROM FURFURAL BY SEVERAL ROUTES



X	Yield, %			Over-all yield, % based on furfural	Ref.
	step A	step B	step C		
$(C_2H_5)_2$	15–20	75–80	35–50	4–8	76, 103, 77, 93
$-CH_2$	—	70	—	—	104
$\vert$	70	<95	10 (29)*	7 (19)	81
$-CH_2$	83	<95	10 (29)*	8 (23)	105
$(OAc)_2$	34	74 (?)†	120 (?)†	—	71, 106
	54	24	35	5	93
	60	78	63	30	105

* 66% of the acetal was recovered unchanged. Therefore yield amounts to 29% based on unrecovered acetal.

† The constants reported by Scheibler *et al.*[71, 106] suggest that the products were quite impure. Therefore the yields are highly questionable, especially that in step C.

[99] Scheibler, Jeschke and Beiser, *J. prakt. Chem.*, **137**, 322 (1933).

[100] Van Campen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).

[101] Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," Madison, University of Wisconsin Press (1937).

[102] Bremner, Coats, Robertson and Allan, *J. Chem. Soc.*, **1949**, Suppl. Issue, No. 1, S25.

Reaction with Ammonia, Amines and Other Nitrogen Compounds

Hydrofuramide and Furfurin. Treatment of furfural with strong aqueous ammonia[a] gives rise to hydrofuramide, I, m.p. 117°,[107, 108, 109, 110] frequently referred to in the early literature as furfuramide. Its formation in this manner was the basis for an early analytical method for furfural.[111, 112] Reaction velocity data are reported by Nikitin[113]; thermal data by Delepine.[114]

Hydrofuramide is relatively insoluble in cold water, and soluble in alcohol, ether and many other organic solvents. In boiling water, or aqueous acids, it is partially decomposed into its generators, and in part is transformed into a black, thermoplastic resin. When treated with hydrogen sulfide it gives a polymeric thiofurfural[115]; with thiophenol in boiling dioxane it is partially decomposed with liberation of ammonia and formation of N-[furyl(phenylmercapto)methyl]furfurylideneimine, C_4H_3O—CH=N—$CH(SC_6H_5)$—C_4H_3O, m.p. 49°.[116] For reaction of hydrofuramide with mustard oil derivatives, see Schiff.[108] Catalytic reduction produces a mixture of mono- and difurfurylamines.[117]

Hot, aqueous alkali converts hydrofuramide into a resinous mass from which the isomeric furfurin (2,4,5-trifurylimidazoline, II) may be isolated[108, 109] (see also [119]). Furfurin, m.p. 116–117°, has also been obtained, in low yield, by passing ammonia into furfural at elevated temperature,[120, 121] and *quantitatively* by simply dissolving hydrofuramide in

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[a] From furfural, dichloroacetaldehyde and aqueous ammonia Spasov and Ivanov[118] have recently reported the isolation of a crystalline product, m.p. 111–112°, to which they assigned the structure C_4H_3O—CH=N—CH(OH)—$CHCl_2$.

[103] Covert, Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).

[104] Dickey and McNally (to Eastman Kodak Co.), U. S. Pat. 2,153,134 (1939); *C. A.*, **33**, 5204 (1939).

[105] The Quaker Oats Company, unpublished work.

[106] Scheibler, Sotscheck and Friese, *Ber.*, **58**, 1961 (1925).

[107] Fownes, *Ann.*, **54**, 52 (1845).

[108] Schiff, *Ber.*, **10**, 1186 (1877).

[109] Bieler and Tollens, *Ann.*, **258**, 110 (1890).

[110] Hartley and Dobbie, *J. Chem. Soc.*, **73**, 598 (1898).

[111] Günther and Tollens, *Ber.*, **23**, 1751 (1890).

[112] Stone, *Am. Chem. J.*, **13**, 73 (1891); *Ber.*, **23**, 3791 (1890).

[113] Nikitin and Abramova, *J. Gen. Chem. U.S.S.R.*, **9**, 1347 (1939); *C. A.*, **34**, 1543 (1940).

[114] Delepine, *Compt. rend.*, **126**, 343 (1898); *Ann. chim.*, (7), **16**, 221 (1899).

[115] Cahours, *Ann.*, **69**, 82 (1849).

[116] Dougherty and Taylor, *J. Am. Chem. Soc.*, **55**, 4588 (1933).

[117] Winans, *J. Am. Chem. Soc.*, **61**, 3566 (1939).

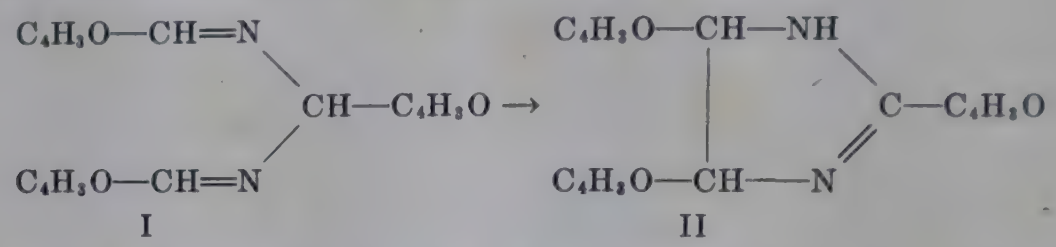
[118] Spasov and Ivanov, *Annuaire univ. Sofia, Faculté sci.*, **45, Livre 2**, 157 (1947–1948); *C. A.*, 44, 3937 (1950).

[119] Radziszewski, *Ber.*, **10**, 321 (1877).

[120] Bertaginini, *Ann.*, **88**, 127 (1853).

[121] Bruins, *Iowa State Coll. J. Sci.*, **10**, 51 (1935).

liquid ammonia and concentrating the resulting solution until crystallization occurs.[122] When the latter reaction is carried out in the presence of ammonium chloride[122], it appears that there is formed a small amount of the elusive furfurylideneimine, $C_4H_3O—CH=NH$, earlier reported in the form of the hydrochloride, m.p. 52°, by the action of hydrogen chloride on hydrofuramide in dry benzene[123] (see also p. 376). For a report on the crystal form of furfurin, see Dauber.[124]



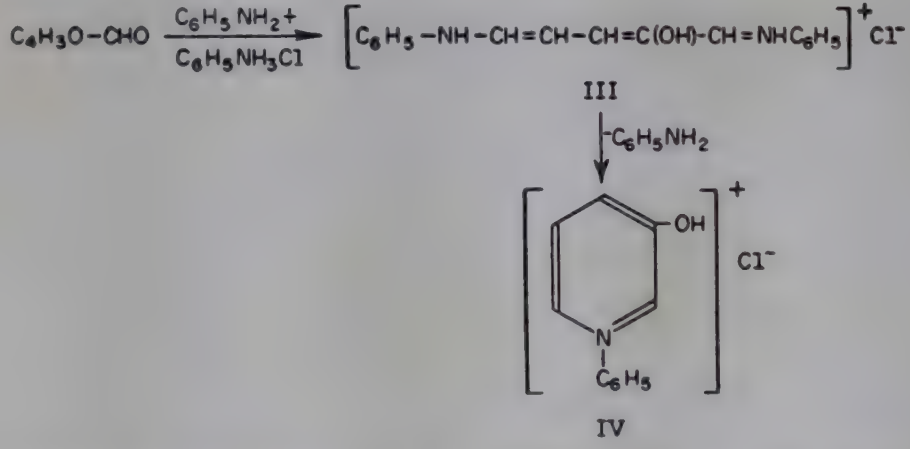
As a base, furfurin forms salts [125, 126] of which the nitrate has been shown to exist in two forms.[122] With acetic anhydride[108] or acetyl chloride[127] it gives a monoacetyl derivative, m.p. 248° (dec.) which is unaffected by methyl iodide, indicating only one replaceable hydrogen atom. This is in agreement with the work of Davidson[128] who observed that alkylation of furfurin with ethyl and pentyl iodides introduced only one alkyl radical; see, however, Ramsay[129] and Gerstl.[130] Nitrosofurfurin, m.p. 112°.[131]

Treatment of furfurin with an excess of potassium amide in liquid ammonia results in the liberation of hydrogen. However, whereas the benzene analog, amarine, is converted into triphenylimidazole (lophine) under these conditions, it was not possible to isolate its counterpart in the furan series.[122] Catalytic hydrogenation of furfurin over nickel on kieselguhr produces 2,4,5-tri(tetrahydrofuryl)imidazoline (hydrofurfurin; b.p. 200–205° (4 mm.); picrate, m.p. 202–203°), the carbon to nitrogen double bond being resistant to hydrogenation even at a temperature as high as 200°.[132] Curiously, Grossman[133] reports the formation of N,N′-difurfurylidene-1,2-difurylethylenediamine, m.p. 174°, when furfurin is reduced with sodium in alcohol.

[122] Strain, *J. Am. Chem. Soc.*, **52**, 1216 (1930).
[123] Busch and Wolff, *J. prakt. Chem.*, **60**, 198 (1899).
[124] Dauber, *Ann.*, **74**, 200 (1850).
[125] Karmrodt, *Ann.*, **81**, 164 (1852).
[126] Guareschi, *Giornale della Reale Accademia di Medicina*, **1891**, separate reprint by author, 20 pages; *Chem. Centr.*, **1891**, II, 620.
[127] Bahrmann, *J. prakt. Chem.*, **27**, 295 (1883).
[128] Davidson, *Edinburgh Philosophical J.*, New Series, **II**, 284; *Chem. Centr.*, **1855**, 851.
[129] Ramsey, *Chem. Centr.*, **1879**, 285.
[130] Gerstl, *Ber.*, **11**, 1836 (1878).
[131] Schiff, *Ber.*, **11**, 1250 (1878).
[132] Winans and Adkins, *J. Am. Chem. Soc.*, **55**, 2051 (1933).
[133] Grossman, *Ber.*, **22**, 2305 (1889).

The successful conversion of furfurin into isofurfurin (m.p. 143°), analogous to the amarine-isoamarine rearrangement, is the subject of a paper by Millington and Hibbert.[134] Strain,[122] however, was unable to effect such a transformation.

Condensations with Amines and Ammonium Salts. Equimolecular proportions of furfural and primary aliphatic amines condense with loss of water to produce the aldimine, or Schiff's base, $C_4H_3O—CH=NR$. Many aromatic amines behave similarly, but under certain conditions, a much more complex reaction can ensue. Thus, furfural and aniline give rise to the anil, but if the aldehyde is treated with aniline hydrochloride, the furan ring is ruptured and two moles of the amine are consumed. This, and related cleavage reactions involving furfural and ammonium salts are considered in detail elsewhere (p. 669) and will be discussed only briefly here. In the experiment mentioned above, the product obtained is the dianil salt, β-hydroxyglutaconaldobisphenylimine hydrochloride, III, a purple, crystalline compound which dyes[b] red on cotton, wool and silk. On heating III in nitrobenzene, or other suitable solvent, a black, tarry mass is obtained, from which the colorless 1-phenyl-3-hydroxypyridinium chloride, IV, may be isolated. Similar products have been synthesized from *p*-toluidine hydrochloride and a variety of other aromatic amines and their salts (see Chapter 14).



Furfurylidenebis(dimethylamine): $C_4H_3O—CH[N(CH_3)_2]_2$; yellow-brown liquid, from furfural and two moles of dimethylamine with cooling. With methyl iodide it is converted into **furfurylidenebis(trimethylammonium iodide)** from which the hydroxide, m.p. 174°, has been obtained.[137]

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[b] Schiff[134a] likewise obtained dye bases by the action of phosphorus pentachloride on furfural and subsequently reacting with aniline. He postulated intermediate formation of the unknown furfurylidene dichloride, $C_4H_3O—CHCl_2$.

[134] Millington and Hibbert, *Chem. News*, **82**, 46 (1900).

[134a] Schiff, *Ber.*, **19**, 2153 (1886).

[135] Emling, Beatty and Stevens, *J. Am. Chem. Soc.*, **71**, 703 (1949).

[136] Schwabbauer, *Ber.*, **35**, 410 (1902).

[137] Litterscheid, *Ann.*, **335**, 368 (1904).

N,N-furfurylidenedipiperidine: $C_4H_3O{-}CH\left(N\!\!<\!\!\begin{smallmatrix}\\ \\ \\ \\ \\ \end{smallmatrix}\!\!>\!\!S\right)_2$; b.p. 157–158° (14 mm.); from furfural and two moles of piperidine.[144]

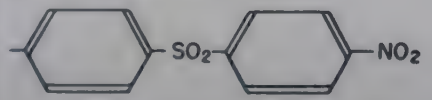
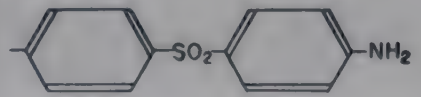
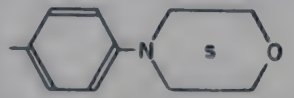
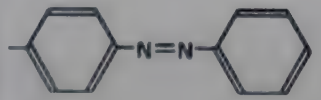
N,N-furfurylidenedimorpholine: $C_4H_3O{-}CH\left(N\!\!<\!\!\begin{smallmatrix}\\ \\ \\ \\ \\ \end{smallmatrix}\!\!>\!\!S\!\!<\!\!\begin{smallmatrix}\\ \\ \\ \\ \\ \end{smallmatrix}\!\!>\!\!O\right)_2$; I; m.p. 120–120.5°; on heating furfural in alcohol with two molecular proportions of morpholine. With equimolecular proportions at 0°, a 1:1 addition compound, $C_9H_{13}O_3N$, m.p. 49–50° (dec.) is formed which decomposes on standing to give furfural and I.[177]

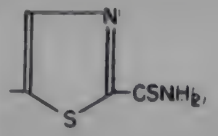
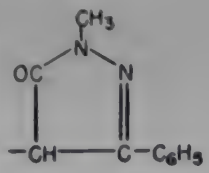
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[140] Adkins and Winans, U. S. Pat. 2,175,585 (1939); *C. A.*, **34**, 779 (1940).
[141] Wallach and Jenckel, *Ann.*, **269**, 369 (1892).
[142] Wallach and Lorentz, *Ann.*, **268**, 197 (1892).
[143] Leach, *J. Chem. Soc.*, **91**, 1 (1907).
[144] de Chalmot, *Ann.*, **271**, 11 (1892).
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[148] Umnova, *J. Gen. Chem. U.S.S.R.*, **10**, 569 (1940); *C. A.*, **34**, 7902 (1940).
[149] Schiff, *Ber.*, **11**, 1840 (1878).
[150] Schiff, *Ann.*, **201**, 355 (1880).
[151] Winans, British Pat. 497,778 (1938); *C. A.*, **33**, 4078 (1939).
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[154] Ehrhardt, *Ber.*, **30**, 2012 (1897).
[155] Fischer, Balling and Aldinger, *J. prakt. Chem.*, **100**, 86 (1919).
[156] Freund and Immerwahr, *Ber.*, **23**, 2845 (1890).
[157] Schlögl, *J. prakt. Chem.*, **88**, 251 (1913).
[158] Heuck, *Ann.*, **255**, 188 (1889).
[159] Vignoli and Sicé, *Bull. soc. chim.*, **12**, 877 (1945).
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[161] Jain, Mirchandani, Iyer and Guha, *J. Indian Chem. Soc.*, **24**, 191 (1947); *C. A.*, **43**, 2592 (1949).
[162] Fel'dman and Syrkin, *Zhur. Obshchei Khim. J. Gen. Chem.* **19**, 1369 (1949); *C. A.*, **44**, 1051 (1950).
[163] Dugan and Haendler, *J. Am. Chem. Soc.*, **64**, 2502 (1942).
[164] Betti, *Gazz. chim. ital.*, **28**, **I**, 241 (1898).
[165] Schiff, *Ber.*, **19**, 847 (1886).
[166] Cooper and Nuttall, *J. Chem. Soc.*, **101**, 1074 (1912).
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[168] Hayes, Gever and Orcutt, *J. Am. Chem. Soc.*, **72**, 1205 (1950).
[169] Ridi, *Gazz. chim. ital.*, **71**, 462 (1941); *C. A.*, **37**, 1123 (1943).
[170] Hellsing, *Ber.*, **33**, 1774 (1900).
[171] Wrede, *Ann.*, **352**, 198 (1907).
[172] Rameau, *Rec. trav. chim.*, **57**, 192 (1938).
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[174] Reuland, *Ber.*, **22**, 3011 (1889).
[175] Schiff and Vanni, *Ann.*, **258**, 363 (1890).
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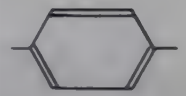
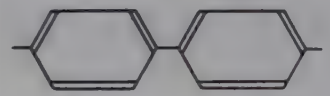
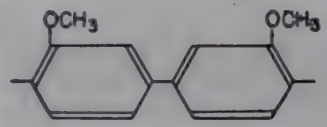
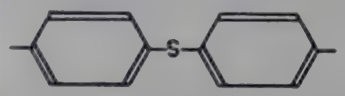
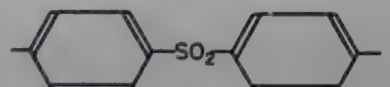
Reagent	$C_4H_3O—CHO + H_2NR \rightarrow C_4H_3O—CH=NR$		Ref.
	R	Physical constants of products (°C.)	
Methylamine	CH_3	b.p. 53 (16 mm.), 62–65 (25 mm.) n_D^{20} 1.5269; d_4^{20} 1.025	135, 136, 137
Ethylamine	C_2H_5	b.p. 67 (18 mm.) n_D^{20} 1.5170; d_4^{20} 0.988	135, 136, 138
2-Hydroxyethylamine	$HOCH_2CH_2$	b.p. 120–122 (2 mm.) n_D^{25} 1.5562; d_{15}^{15} 1.1562	139
n-Propylamine	C_3H_7	b.p. 87–88 (21 mm.) n_D^{20} 1.5105; d_4^{20} 0.967	135
n-Butylamine	C_4H_9	b.p. 90 (13 mm.), 110–115 (32 mm.) n_D^{20} 1.5057; d_4^{20} 0.950	135, 140
n-Pentylamine	C_5H_{11}	b.p. 104–105 (10 mm.) n_D^{20} 1.5024; d_4^{20} 0.940	135
Cyclohexylamine		b.p. 100–102 (2 mm.) n_D^{25} 1.5354; d_{15}^{15} 1.0296	139
Fenchylamine	—	b.p. 167 (16 mm.)	141
Pinylamine	—	m.p. 80–81	142
Pinene nitrolamine	—	m.p. 164	143
Benzylamine	$C_6H_5CH_2$	b.p. 129–131 (2 mm.), 155 (19 mm.)	140, 144, 145
α-(2-Hydroxynaphthyl)-benzylamine	$C_6H_5CH(C_{10}H_6—OH)$	m.p. 115–116	146
Aniline	C_6H_5	m.p. 58 b.p. 122–123 (2 mm.)	144, 147, 148
o-Toluidine	$C_6H_4CH_3$	m.p. 54–55 b.p. 171–172 (19 mm.)	144, 148
p-Toluidine	$C_6H_4CH_3$	m.p. 43–44	144
p-Aminophenol	C_6H_4OH	m.p. 180–182, 187–187.5	149, 150, 151, 140; see also 152, 153
p-Phenetidine	$C_6H_4OC_2H_5$	m.p. 72–73	154

TABLE 4—*Continued*

Reagent	R	Physical constants of products (°C.)	Ref.
o-Chloroaniline	C_6H_4Cl	m.p. 66	155
p-Chloroaniline	C_6H_4Cl	m.p. 48–50	155
p-Nitroaniline	$C_6H_4NO_2$	m.p. 139–140	155
m-Nitro-*o*-toluidine	$C_6H_3(CH_3)(NO_2)$	m.p. 130	155
p-Nitro-*o*-toluidine	$C_6H_3(CH_3)(NO_2)$	m.p. 75	155
p-Aminophenylacetonitrile	$C_6H_4CH_2CN$	m.p. 93–94	156
p-Aminodimethylaniline	$C_6H_4N(CH_3)_2$	m.p. 100–101	155
p-Aminophenylglycine	$C_6H_4(NHCH_2COOH)$	m.p. 135	157
p-Aminophenyloxamic acid	$C_6H_4(NHCO—COOH)$	m.p. 130	157
N-phenyl-*p*-phenylenediamine	C_6H_4-NHC_6H_5	m.p. 129	158
Sulfanilamide	$C_6H_4(SO_2NH_2)$	m.p. 208 (dec.)	159
4-Nitrophenyl-4-aminophenyl sulfone		m.p. 150	160, 161
4-Aminophenyl sulfone		m.p. 153	160, 161; see also 162
p-Morpholinoaniline		m.p. 208–209	163
4-Aminoazobenzene		m.p. 129–130	164
2-Naphthylamine	$C_{10}H_7$	m.p. 84, 85	165; see also 166, 167
2-Aminopyridine	C_5H_4N	m.p. 54.5–55	168; see also 169
2-Aminothiazole	C_3H_2SN	m.p. 61.5–63	168

Reagent	R	Physical constants of products (°C.)	Ref.
5-Amino-2-thiazole-carbonthionoamide (chrysean)		m.p. 184	170
1-Methyl-3-phenyl-4-amino-5-pyrazolone		m.p. 180	171

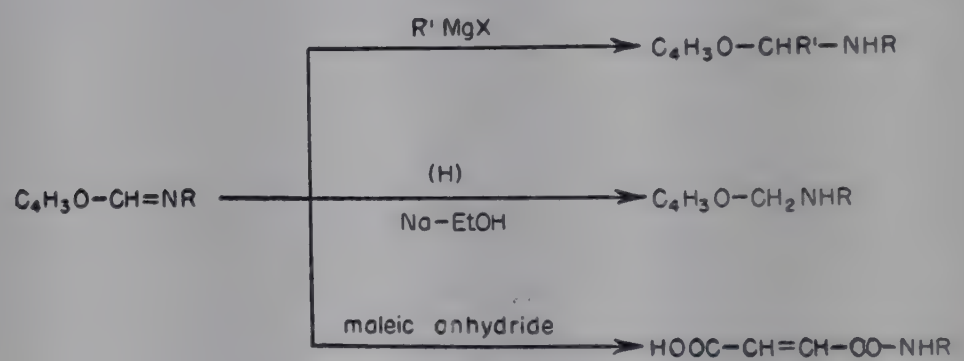
$$C_4H_3O{-}CHO + H_2N{-}R{-}NH_2 \rightarrow C_4H_3O{-}CH{=}N{-}R{-}N{=}CH{-}C_4H_3O$$

	—R—		
Ethylenediamine	—CH_2—CH_2—	m.p. 53–54 b.p. 205 (30 mm.)	172
p-Phenylenediamine		m.p. 164–165	140
Benzidine		m.p. 212–213, 231–232	154; see also 173, 150, 174, 140
o-Tolidine		m.p. 188–189, 192	154, 175
o-Dianisidine		m.p. 181–182	154
4-Aminophenyl sulfide		m.p. 103–104	176
4-Aminophenyl sulfone		m.p. 300 (dec.)	162

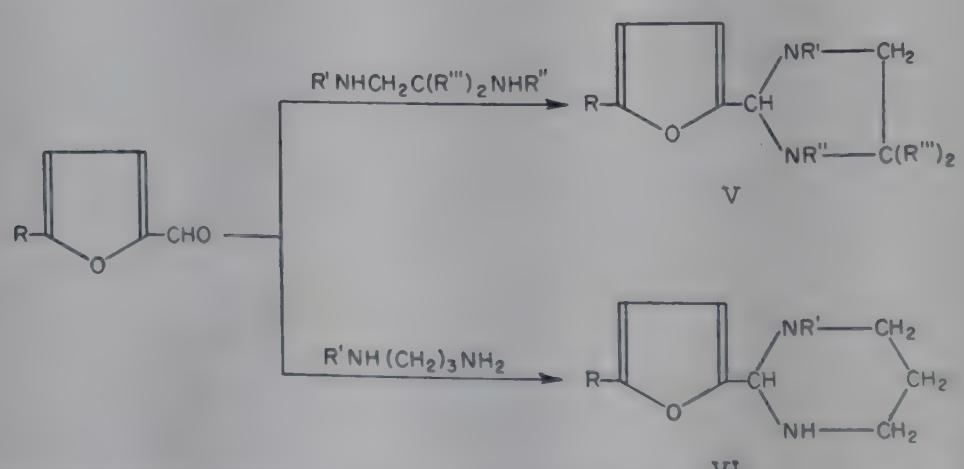
Furfurylidenebis(2-pyridylamine): $C_4H_3O—CH(NH—C_5H_4N)_2$; m.p. 83–84.5° (dependent upon rate of heating); by evaporation of an alcoholic solution of two moles of 2-aminopyridine and one mole of furfural. Appears to undergo disproportionation when heated in alcohol or benzene with formation of 2-aminopyridine and the furfurylidene azomethine of the latter[168] (see also [169, 178]).

Furfurylidenebis(2-thiazolylamine): $C_4H_3O—CH(CH—C_3H_2SN)_2$; m.p. 112-114° (dependent on rate of heating) from furfural and 2-aminothiazole as in the preceding preparation.[168]

The Grignard reagent adds normally to the double linkage of the aldimines to give, on subsequent hydrolysis, the appropriate secondary amine.[135, 168] Schwabbauer[136] (see also [179, 148]) reports N-methylfurfurylamine by reduction of furfurylidenemethylamine with sodium in alcohol. With maleic anhydride in ether, the latter is split to N-methylmaleamic acid.[180] For insecticidal action of several of the aldimines, see West.[139] Plastic products derived from furfural and amines are discussed elsewhere (p. 781).



With aliphatic 1,2-diamines, furfural gives rise to the appropriately substituted imidazolidines (V). 2-Furylhexahydropyrimidines (VI) are formed from the aldehyde and 1,3-diamino compounds.



[178] Lincoln, Heinzelmann and Hunter, *J. Am. Chem. Soc.*, **71**, 2902 (1949).
[179] Braun and Braunsdorf, *Ber.*, **54**, 2081 (1921).
[180] Herz, *J. Am. Chem. Soc.*, **67**, 1854 (1945).

1-*i*-Propyl-2-furyl-4,4-dimethylimidazolidine: V (R,R″=H; R′=*i*-C_3H_7; R‴=CH_3); b.p. 128–130° (22 mm.), d_4^{20} 0.9805, n_D^{20} 1.4863. In 73 per cent yield from furfural and N-(2-aminoisobutyl)isopropylamine.[181]

2-Furyl-1,3-diisobutylimidazolidine: V (R,R‴=H; R′,R″=*i*-C_4H_9); b.p. 100–120° (22 mm.), $n_D^{24.5}$ 1.4750. From furfural and 1,2-bis(isobutylamino)ethane. Related products were derived from the latter and 5-methylfurfural (V; R=CH_3; R′,R″,R‴ same as above; b.p. 130–155° (22 mm.), n_D^{24} 1.4744); and 5-(hydroxymethyl)furfural (V; R=CH_2OH; R′,R″,R‴ same as above; m.p. 56–57°).[172]

1-Phenyl-2-furyl-4,4-dimethylimidazolidine: V (R,R″=H; R′=C_6H_5; R‴=CH_3); b.p. 157–159° (4 mm.), n_D^{20} 1.5764. In 70 per cent yield from furfural and N-(2-aminoisobutyl)aniline.[181]

2-Furyl-1,3-dibenzylimidazolidine: V (R,R‴=H; R′,R″=benzyl); m.p. 74°. From furfural and N,N′-dibenzylethylenediamine. Related products were similarly prepared using 5-methylfurfural (V, R=CH_3; R′,R″,R‴ same as above; m.p. 77–78°) and 5-(hydroxymethyl)furfural (V, R=CH_2OH; R′,R″,R‴ same as above; m.p. 127°[182]).

2-Furyl-1,3-bis(*p*-methoxybenzyl)imidazolidine: V (R,R‴=H; R′,R″=*p*-$C_6H_4(OMe)CH_2$); m.p. 76°; from furfural and N,N′-bis(*p*-methoxybenzyl)ethylenediamine. Related derivatives, m.p. 84 and 108°, respectively, were derived from 5-methyl- and 5-(hydroxymethyl)furfural.[172]

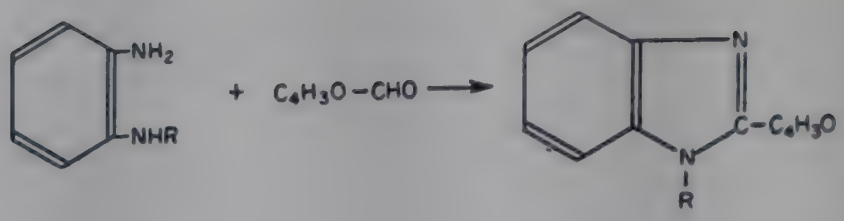
2-Furyl-1,3-bis(2′-phenethyl)imidazolidine: V (R,R‴=H; R′,R″=$C_6H_5CH_2CH_2$); b.p. 240–255° (15 mm.), n_D^{17} 1.5644. From furfural and N,N′-diphenethylethylenediamine. The latter and 5-methylfurfural reacted in the same manner to give the expected homolog, b.p. 250–265° (15 mm.), n_D^{12} 1.5680.[172]

N-*i*-propyl-2-furylhexahydropyrimidine: VI (R=H; R′=*i*-C_3H_7); b.p. 122–123° (5 mm.). In 64 per cent yield from furfural and N-*i*-propyl-1,3-propanediamine.[183]

When furfural is heated with *o*-phenylenediamine or its N-monoalkyl derivatives in the presence of aqueous cupric acetate, 2-furylbenzimidazoles, VII, are obtained[184] (see also [185]). VII (R=H) has also been obtained from anhydro-D-xylo-, lyxo-, and ribobenzimidazoles by refluxing these compounds[c] in acetic anhydride.[186] These products, and also the several furylimidazolopyridines synthesized by Weidenhagen,[187] may be looked upon as cyclic derivatives of 2-furamidine (p. 536). For early work on the condensation of furfural with aromatic *o*-diamines, see Ladenburg *et al.*[188, 189, 190] (see also [191]). Related to this is the reaction of furfural with

[c] The D-arabo isomer failed to give furylbenzimidazole.[186]

[181] Riebsomer, *J. Org. Chem.*, **15**, 237 (1950).
[182] Lob, *Rec. trav. chim.*, **55**, 859 (1936).
[183] Riebsomer and Morey, *J. Org. Chem.*, **15**, 245 (1950).
[184] Weidenhagen, *Ber.*, **69**, 2263 (1936).
[185] Weidenhagen and Wegner, *Ber.*, **71**, 2124 (1938).
[186] Huebner, Lohmar, Dimler, Moore and Link, *J. Biol. Chem.*, **159**, 503 (1945).
[187] Weidenhagen, Train, Wegner and Nordström, *Ber.*, **75**, 1936 (1942).
[188] Ladenburg, *Ber.*, **11**, 590 (1878).
[189] Ladenburg and Englebrecht, *Ber.*, **11**, 1653 (1878).
[190] Ladenburg and Rügheimer, *Ber.*, **11**, 1656 (1878).
[191] Hinsberg, *Ber.*, **20**, 1585 (1887).

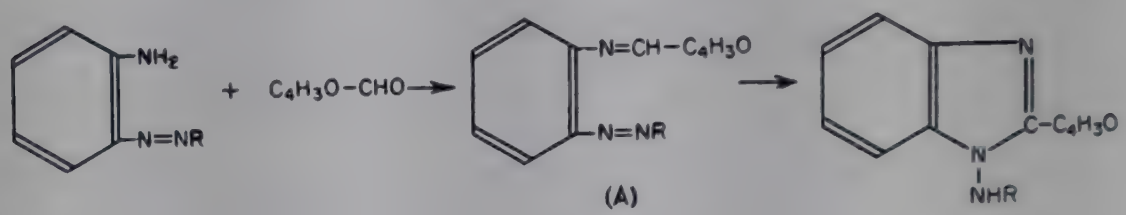


VII

R = H; m.p. 285-286°

R = CH_3; m.p. 56°

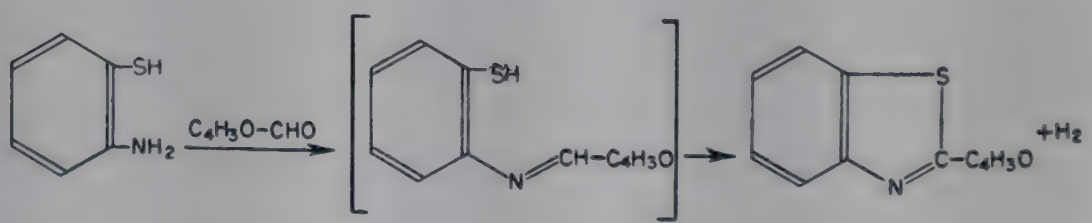
o-aminoazo compounds, giving rise to N-arylamino-2-furylbenzimidazoles, VIII, by virtue of rearrangement of the intermediate Schiff's base, A, in boiling glacial acetic acid[192] (see also [193]).



(A)

VIII

o-Aminophenyl mercaptan reacts with furfural in acetic acid to give 2-furylbenzothiazole, IX, in 36 per cent yield, a reaction which is presumed to proceed by way of the intermediate anil, B.[194] With zinc *o*-amino-



(B)

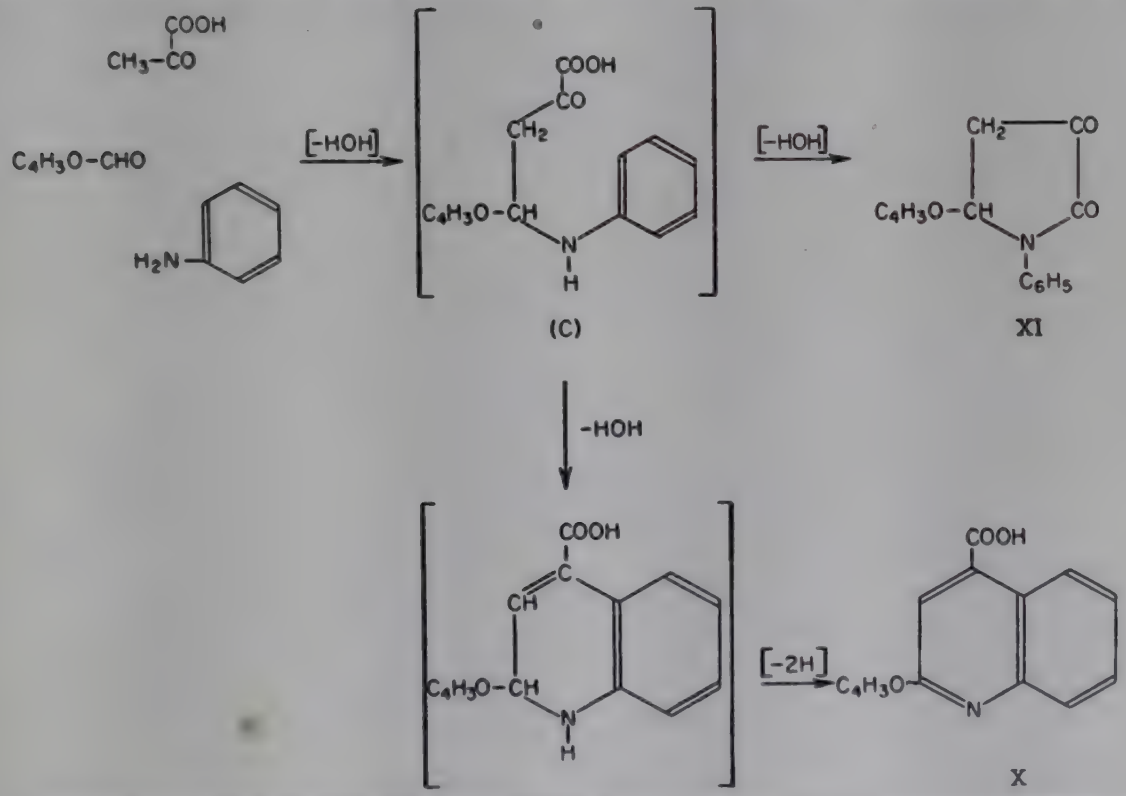
IX

phenyl mercaptide, furfural gives rise to the red, zinc salt (decomposition 232–234°) of the dianil, $(C_4H_3O—CH=NC_6H_4S)_2Zn$, which is converted into IX on refluxing for ten minutes with glacial acetic acid. *o*-Furfurylideneaminophenyl disulfide, $(C_4H_3O—CH=NC_6H_4S)_2$, m.p. 134.5°, from furfural and *o*-aminophenyl disulfide, is also convertible into IX when refluxed with an equal weight of furfural.[195]

Furfural, aniline and pyruvic acid condense in warm alcohol with formation of 2-furylcinchoninic acid (2-furyl-4-carboxyquinoline), X, which on heating above its melting point loses carbon dioxide to give 2-furylquino-

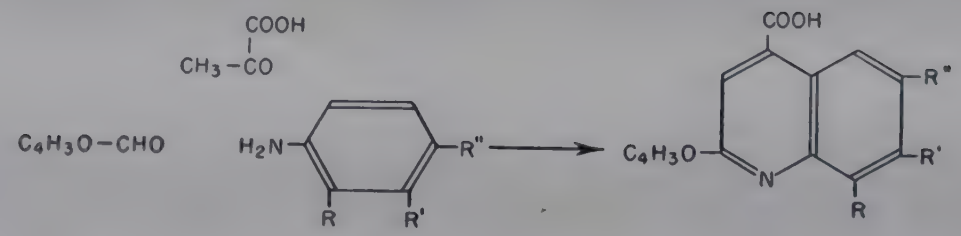
[192] Fischer, *J. prakt. Chem.*, **104**, 102 (1922); **107**, 16 (1924).
[193] Goldschmidt and Poltzer, *Ber.*, **24**, 1000 (1891).
[194] Bogert and Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925).
[195] Bogert and Naiman, *J. Am. Chem. Soc.*, **57**, 1529 (1935).

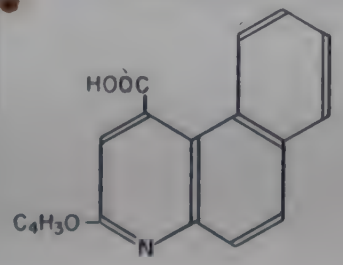
line, m.p. 92°.[196] A variety of substituted furylcinchoninic acids have been synthesized in similar manner from primary aromatic amines other than aniline. The course of the condensation reaction is apparently dependent upon several factors, one of which may be the nature of the solvent medium. Thus, if the reaction described above is carried out in *cold* alcoholic solution, the product obtained is the anil (m.p. 185°) of 1-phenyl-5-furyl-2,3-pyrrolidinedione, XI[196] (see also [205]). Related to this is the formation of 1-phenyl-5-furyl-4-acetyl-2,3-pyrrolidinedione, m.p. 190° (dec.), from furfural, aniline and acetonyloxalic ester in boiling benzene.[206] Borsche[205] has formulated the scheme illustrated below whereby I and II have their origin in a common intermediate, C, a scheme which is consistent with Doebner's[196] observation that XI is transformed into X by heating with alcohol. One would anticipate that, as a lactam, XI would undergo alcoholysis under these conditions with regeneration of C (in form of its ester), so that the net effect of conducting the over-all reaction in alcohol at elevated temperature would be to favor formation of X at



[196] Doebner, *Ann.*, **242**, 265 (1887).
[197] Ciusa, *Gazz. chim. ital.*, **52**, II, 43 (1922); *C. A.*, **17**, 1478 (1923).
[198] Ciusa and Bellino, *Gazz. chim. ital.*, **66**, 452 (1936); *C. A.*, **31**, 3487 (1937).
[199] Maxim and Petrascu, *Compt. rend. acad. sci. Roumanie*, **8**, 65 (1946–47); *C. A.*, **43**, 1411 (1949).
[200] Mangini, *Ann. chim. applicata*, **27**, 386 (1937); *C. A.*, **32**, 2287 (1938).
[201] Borsche and Wagner-Roemmich, *Ann.*, **544**, 287 (1940).
[202] Ciusa and d'Amato, *Gazz. chim. ital.*, **67**, 776 (1937); *C. A.*, **32**, 4586 (1938).
[203] Mangini, *Riv. biol.*, **22**, 482 (1937); *C. A.*, **32**, 3900 (1938).
[204] Musajo, *Gazz. chim. ital.*, **60**, 673 (1930); *C. A.*, **25**, 955 (1931).
[205] Borsche, *Ber.*, **41**, 3884 (1908).
[206] Schering, German Pat. 280,971 (1914); *C. A.*, **9**, 1829 (1915).

Table 5. 2-Furylcinchoninic Acids



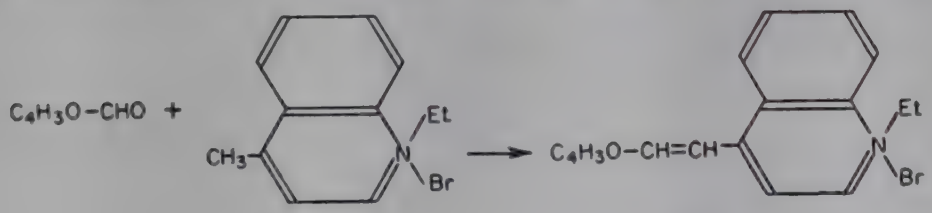
Amine (A)	Product (B)	M.p. (°C.)	Ref.
Aniline	R,R′,R″ = H	210–215, 227	196; see also 197, 198, 199
o-Toluidine	R = CH_3; R′,R″ = H	248	200
m-Toluidine	R′ = CH_3; R,R″ = H	272	200
p-Toluidine	R″ = CH_3; R,R′ = H	253	200
m-Hydroxyaniline	R′ = OH; R,R″ = H	dec. 311–312	201
p-Hydroxyaniline	R″ = OH; R,R′ = H	302–305	202
o-Anisidine	R = OCH_3; R′,R″ = H	230–231	203
p-Anisidine	R″ = OCH_3; R,R′ = H	240, 242–243	202, 203
o-Phenetidine	R = OC_2H_5; R′,R″ = H	150–151 (dec.) (?) **ethyl ester,** 67	202
p-Phenetidine	R = OC_2H_5; R,R′ = H	215–216 (dec.), 218–219	202, 203
2-Naphthylamine		278	204

the expense of XI. Pharmacological tests indicate that the activity of the furylcinchoninic acids is only 65–75 per cent of that of atophan, 2-phenylcinchoninic acid.[200, 207, 203]

In his study of the reaction of aldehydes with tertiary amines, Fischer[208, 209] condensed furfural with dimethylaniline in the presence of zinc chloride. This work was repeated by Renshaw and Naylor[210] (see also [211]) who report formation of the furan analog of leuco malachite green.[d] Oxidation produces a stable dye which gives gray-blue shades on silk, wool and mordanted cotton. The related analog of leuco brilliant green, furylbis(*p*-diethylaminophenyl)methane, m.p. 78°, was similarly obtained from furfural and diethylaniline by Mahood and Aldrich[213] who report that furfural condenses less readily with tertiary amines than does benzaldehyde; and that in malachite green, replacement of a phenyl group by furyl lowers the stability of the dye.

From furfural and *m*-tolylenediamine sulfate, Mahood and Harris[214] (see also [211]) report the synthesis of the furan analog of benzoflavine, 3,6-diamino-2,7-dimethyl-9-furylacridine, a dark-brown, somewhat hygroscopic powder. The rosamine analog has also been prepared by condensation of furfural with *m*-dimethylaminophenol.[211]

Photosensitive dyes derived from furfural and heterocyclic ammonium salts are described by Katayanagi.[215] Thus, furfural condenses with 4-methyl-N-ethylquinolinium bromide (lepidine ethobromide) to give the furylvinyl derivative, XII, orange plates, m.p. 162°. 4-(2-Furylvinyl)-



XII

6-methoxy-N-methylquinolinium iodide, orange columns, m.p. 249°, is obtained similarly from the appropriate lepidine derivative; and 2-(2-furylvinyl)benzothiazole ethobromide, greenish-yellow, m.p. 182°, from

[d] For related dyes prepared from 5-chloro-, 5-bromo-, and 5-nitrofurfural, see Hewlett.[212]

[207] Mangini, *Ann. chim. applicata*, **28**, 34 (1938); *C. A.*, **32**, 7664 (1938).

[208] Fischer, *Ber.*, **10**, 1623 (1877).

[209] Fischer, *Ann.*, **206**, 83 (1881).

[210] Renshaw and Naylor, *J. Am. Chem. Soc.*, **44**, 862 (1922).

[211] Orlov and Florova, *J. Applied Chem. U.S.S.R.*, **9**, 2039 (1936); *C. A.*, **31**, 2601 (1937).

[212] Hewlett, *Iowa State Coll. J. Sci.*, **6**, 439 (1932).

[213] Mahood and Aldrich, *J. Am. Chem. Soc.*, **52**, 4477 (1930).

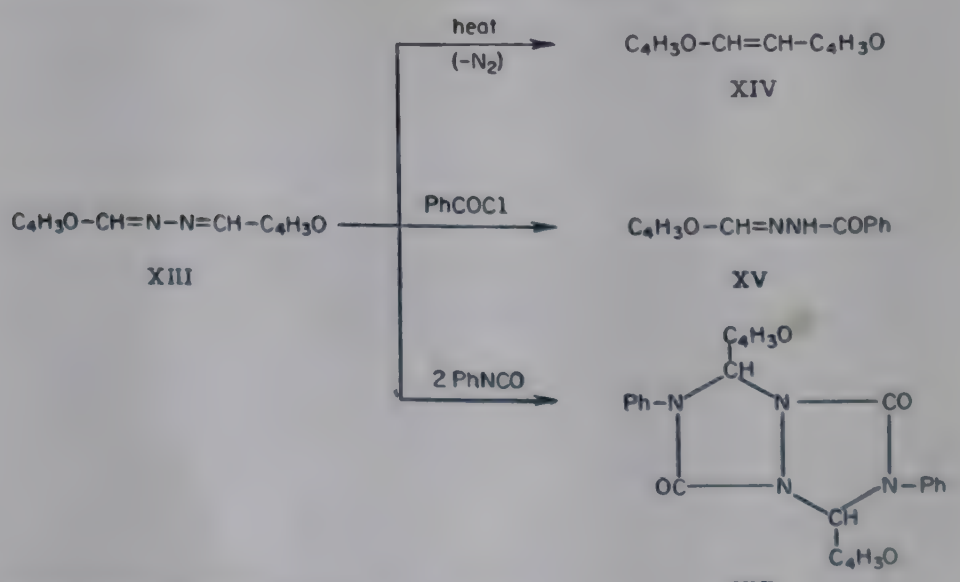
[214] Mahood and Harris, *J. Am. Chem. Soc.*, **46**, 2810 (1924).

[215] Katayanagi, *J. Pharm. Soc. Japan*, **69**, 237 (1949); *C. A.*, **44**, 1987 (1950).

furfural and the quaternary ammonium salt of 2-methylbenzothiazole.[215] Related to the latter are certain thio- and seleno-carbocyanine dyes containing a furan ring which are the subject of a patent to I. G. Farbenindustrie.[216]

Reaction with Hydrazine and Its Derivatives.

Furfural hydrazone, $C_4H_3O—CH=NNH_2$, b.p. 105–110° (*ca.* 12 mm.), is prepared by the action of furfural on hydrazine hydrate[217, 218] (see also [219]). With two molecular proportions of the aldehyde to one of hydrazine, generally as the hydrochloride or sulfate, furfural azine, XIII (m.p. 110–111, 111–112, 115°) is produced[220, 219, 221, 222, 217, 223] (see also [224]). Careful application of heat decomposes the azine with formation of *sym.*-difurylethylene, XIV.[225] Benzoyl chloride replaces one or both furfurylidene radicals depending upon the experimental conditions. If the first possibility happens, the product is furfurylidenebenzohydrazide, XV, which is also obtainable from furfural and benzohydrazide.[221] The bicyclo derivative, XVI, was obtained by reacting furfural azine with phenyl isocyanate, and related products were derived by treatment of XIII with potassium cyanate and with potassium thiocyanate in glacial acetic acid.[226] Thermal studies of binary mixtures indicate eutectic compositions corresponding to 36 per cent XIII and 64 per cent benzaldehyde azine (m.p. 72.8°) and to 68 per cent XIII and 32 per cent 2-thiophenecarbonal azine (m.p. 90.5°).[227] The ultraviolet absorption spectra of furfural azine indicates a relatively large contribution by dipolar structures to the resonance hybrid.[228] The compound absorbs ultraviolet and transmits visible light.



[216] I. G. Farbenindustrie Akt.-Ges., French Pat. 774,410 (1934); *C. A.*, **29**, 2368 (1935).

[217] Wolff, *Ann.*, **394**, 86 (1912).

[218] Kizhner, *J. Russ. Phys.-Chem. Soc.*, **43**, 1563 (1911); *C. A.*, **6**, 1430 (1912).

Furfural ethylidenehydrazone: $C_4H_3O—CH=NN=CHCH_3$; m.p. 109°; by condensation of equimolar proportions of furfural, acetaldehyde and aqueous hydrazine made slightly alkaline with sodium carbonate.[229]

Furfural benzylidenehydrazone: $C_4H_3O—CH=NN=CHC_6H_5$; m.p. 99–100°; from furfural, benzaldehyde and hydrazine as in the preceding preparation.[230]

Furfural phenylhydrazone is obtained in the usual manner from furfural and phenylhydrazine. It is readily soluble in alcohol and ether, and almost insoluble in ligroin. For thermal data, see the work of Landrieu[277]; absorp-

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[219] Kizhner, *J. Gen. Chem. U.S.S.R.*, **1**, 1212 (1931); *C. A.*, **26**, 5299 (1932).
[220] Tebinov, *J. Gen. Chem. U.S.S.R.*, **6**, 528 (1936); *C. A.*, **30**, 5579 (1936).
[221] Minunni and Carta-Satta, *Gazz. chim. ital.*, **29, II**, 467 (1899).
[222] Knöpfer, *Monatsh.*, **30**, 33 (1909).
[223] Grammaticakis, *Bull. soc. chim. France*, **1948**, 979.
[224] Ciusa, *Gazz. chim. ital.*, **36, II**, 97 (1906).
[225] Pascal and Normand, *Bull. soc. chim.* (*4*), **9**, 1059 (1911).
[226] Bailey and McPherson, *J. Am. Chem. Soc.*, **39**, 1322 (1917).
[227] Pascal, *Bull. soc. chim.* (*4*), **15**, 451 (1914).
[228] Blout and Gofstein, *J. Am. Chem. Soc.*, **67**, 13 (1945).
[229] Tebinov, *J. Gen. Chem. U.S.S.R.*, **7**, 656 (1937); *C. A.*, **31**, 5783 (1937).
[230] Tebinov, *J. Gen. Chem. U.S.S.R.*, **6**, 1902 (1936); *C. A.*, **31**, 4315 (1937).
[231] Fischer, *Ann.*, **190**, 67 (1878); *Ber.*, **17**, 572 (1884).
[232] van Ekenstein and Blanksma, *Chem. Weekblad*, **6**, 217 (1909); *Chem. Centr.*, **1909, I**, 1509.
[233] Santi, *Atti. accad. Lincei*, **20, II**, 228 (1911); *C. A.*, **6**, 83 (1912).
[234] Sah and Lei, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 1 (1933); *C. A.*, **27**, 4222 (1933).
[235] Sah, Lei and Shen, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 7 (1933); *C. A.*, **27**, 4222 (1933).
[236] Votoček, Ettel and Koppova, *Bull. soc. chim.*, **39**, 278 (1926).
[237] van Ekenstein and Blanksma, *Rec. trav. chim.*, **24**, 33 (1905).
[238] Bredereck and Fritzsche, *Ber.*, **70**, 802 (1937).
[239] Maaskant, *Rec. trav. chim.*, **55**, 1068 (1936).
[240] Maaskant, *Rec. trav. chim.*, **56**, 211 (1937).
[241] Gardner and Campbell, *J. Am. Chem. Soc.*, **64**, 1378 (1942).
[242] Feist, *Ber.*, **33**, 2098 (1900).
[243] Veibel, *Acta Chem. Scand.*, **1**, 54 (1947).
[244] Amorosa, *Farm sci. e tec Pavia*, **3**, 389 (1948); *C. A.*, **43**, 601 (1949).
[245] Horii, *J. Pharm. Soc. Japan*, **55**, 880 (1935); *C. A.*, **30**, 1763 (1936).
[246] Horii, *J. Pharm. Soc. Japan*, **56**, 53 (1936); *C. A.*, **30**, 4156 (1936).
[247] Tröger and Müller, *J. prakt. Chem.*, **78**, 369 (1908).
[248] Troeger and Piotrowsky, *Arch. Pharm.*, **255**, 233 (1917).
[249] Hewitt and Pope, *J. Chem. Soc.*, **73**, 174 (1898).
[250] Votoček and Lukeš, *Bull. soc. chim.*, **35**, 868 (1924).
[251] Votoček and Lukeš, *Chem. Listy*, **22**, 217 (1928); *C. A.*, **23**, 1400 (1929).
[252] Pope and Hird, *J. Chem. Soc.*, **79**, 1141 (1901).
[253] Blanksma and Witte, *Rec. trav. chim.*, **60**, 811 (1941).
[254] Hartmans, *Rec. trav. chim.*, **65**, 468 (1946).
[255] Clark, Kaye and Parks, *Ind. Eng. Chem., Anal. Ed.*, **18**, 310 (1946).
[256] Bredereck, *Ber.*, **65**, 1833 (1932).
[257] Simon, (a) *Ber.*, **66**, 320 (1933); (b) *Biochem. Z.*, **247**, 171 (1932); *C. A.*, **26**, 3457 (1932).
[258] Purgotti, *Gazz. chim. ital.*, **24, I**, 554 (1894).

TABLE 6. SOME HYDRAZONES OF FURFURAL, 5-METHYLFURFURAL AND 5-(HYDROXYMETHYL)FURFURAL

Reagent	Furfural		5-Methylfurfural		5-(Hydroxymethyl)furfural	
	Derivative, m.p. (°C.)	Ref.	Derivative, m.p. (°C.)	Ref.	Derivative, m.p. (°C.)	Ref.
Arylhydrazines						
Phenyl	96, 97–98	231, 232, 233, 223	liquid	274, 275	138, 140	232, 272
p-Tolyl	105–106	234, 233	—	—	—	—
p-Chlorophenyl	97–98	235	—	—	—	—
o-Iodophenyl	74	236	—	—	—	—
o-Nitrophenyl	155–156	237, 238	—	—	—	—
m-Nitrophenyl	137	237	—	—	—	—
p-Nitrophenyl	137, 151–152, 154–155	237, 241, 239, 240; see also 242, 279a	130, 133	232, 239, 240; see also 242	185	239, 240
p-Carboxyphenyl	210–212	243	—	—	—	—
p-Sulfonamidophenyl	200–202	244	—	—	—	—
p-Thiocyanophenyl	124	245, 246	132	246	—	—
p-Phenylazophenyl	133	247, 248	—	—	—	—
2-Bromo-4-methylphenyl	87	249	—	—	—	—
2,5-Dibromophenyl	104	250	—	—	—	—
3,5-Dibromophenyl	116	250, 251	—	—	—	—
2,6-Dibromophenyl	62	251	—	—	—	—
2-Nitro-4-methylphenyl	165–166	252	—	—	—	—
2-Nitro-5-chlorophenyl	198	240	194	239, 240	192	240
2-Nitro-5-bromophenyl	204	240	164–172	239, 240	195	240
2-Nitro-4-cyanophenyl	204	253	199	253	—	—
2-Cyano-4-nitrophenyl	280	254	151	254	236	254
2,4-Dinitrophenyl	199, 218, 223 (trimorphic)	255; see also 256, 257a, 258, 259	—	257a	184	262, 263, 256

TABLE 6—*Continued*

3-Ethoxy-4,6-dinitrophenyl	225–228	260	199, 237–239	260	177–180	260
3-Chloro-4,6-dinitrophenyl	205	261	—	—	—	—
2,4,6-Trinitrophenyl	246	238, 262, 263; see also 258	218	262, 263	216	262, 263
1-Naphthyl	110.5	233	—	—	—	—
2-Naphthyl	134–135, 137	264, 233	—	—	—	—
2-Fluorenyl	190–191	265	—	—	—	—
Asym. disubstituted hydrazines						
α,α-Diallyl	b.p. 108 (2 mm.)	266	—	—	—	—
α-Benzyl-α-phenyl	138	267, 223	—	—	—	—
α,α-Diphenyl	90	268	—	—	—	—
α-Methyl-α-*o*-nitrophenyl	180	240	61	239, 240	90	240
α-Methyl-α-*p*-nitrophenyl	171	269, 240	120	239, 240	196	240
α-Ethyl-α-*p*-nitrophenyl	150	270	—	—	—	—
α-Methyl-α-(2-nitro-4-chlorophenyl)	134	240	105	239, 240	55–62	240
α-Methyl-α-(2-nitro-4-bromophenyl)	143	240	93	239, 240	90	240
α-Methyl-α-(2,4-dinitrophenyl)	187–189, 190	238, 262, 263, 271	171	262, 263	100	262, 263
α-Ethyl-α-(2,4-dinitrophenyl)	185–186	271	—	—	—	—
α-Methyl-α-(2-nitro-4-cyanophenyl)	184	253	169	253	—	253
α-Methyl-α-(2-cyano-4-nitrophenyl)	225	254	195	254	121	254
α-Methyl-α-(3-ethoxy-4,6-dinitrophenyl)	139	260	173	260	136–137	260
α-Methyl-α-(3-chloro-4,6-dinitrophenyl)	205	261	132, 173	261	108, 126–127	261
α-Methyl-α-picryl	204	262, 263	182	262, 263	196	262, 263
α-Cyano-α-phenyl	98	272	—	—	—	—
α-Methyl-α-(2,4-dinitronaphthyl)	202	260	167, 175	260	122	260
4,4′-Bis(α-methylhydrazinophenyl)methane	201	273	—	—	—	—

tion spectra, see Grammaticakis.[223] With hydroxylamine hydrochloride it is converted into furfural oxime.[278] With maleic anhydride there is produced furfural N-(β-carboxyacrylyl)phenylhydrazone, m.p. 113–114°.[180] Perbenzoic acid acts on furfural phenylhydrazone to produce an oxide, presumably $C_4H_3O—CH(—O—)—N—NHC_6H_5$, which is considerably less stable than the analog derived from benzaldehyde phenylhydrazone under similar conditions.[279] Oxidation with pentyl nitrite gives rise to a mixture from which 2,3-diphenyl-1,4-difurfurylidenetetrazane, XVII, m.p. 135–136° (dec.), has been isolated along with the furohydrazidine derivative, XVIII, m.p. 155.5 or 161°.[280a]

$$C_4H_3O—CH{=}NNHC_6H_5 \xrightarrow{(O)}$$

$$C_4H_3O—CH{=}N—NC_6H_5 \quad | \quad C_4H_3O—CH{=}N—NC_6H_5 \qquad \text{XVII}$$

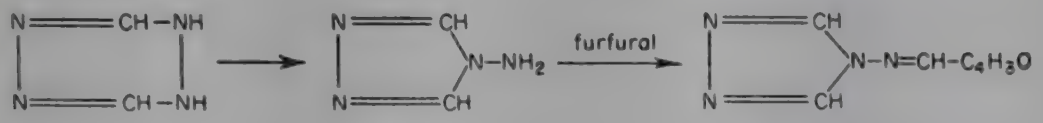
$$+\ C_4H_3O—CH{=}N—N(C_6H_5)—C(=N—NHC_6H_5)—C_4H_3O \qquad \text{XVIII}$$

The polymorphism of furfural 2,4-dinitrophenylhydrazone is discussed by Clark[255] (see also [256, 257a, 257b]). It is unsatisfactory as an identifying derivative, the *p*-nitrophenylhydrazone (m.p. 152°) and the semicarbazone

[259] Roduta and Quibilan, *Rev. filipina med. y farm.*, **27**, 123 (1936); *C. A.*, **31**, 98 (1937).
[260] Robert, *Rec. trav. chim.*, **56**, 909 (1937).
[261] Robert, *Rec. trav. chim.*, **56**, 413 (1937).
[262] Blanksma and Wackers, *Rec. trav. chim.*, **55**, 655 (1936).
[263] Blanksma and Wackers, *Rec. trav. chim.*, **55**, 661 (1936).
[264] Lei, Sah and Kao, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 335 (1934); *C. A.*, **29**, 465 (1935).
[265] Diels, *Ber.*, **34**, 1758 (1901).
[266] Diels, *Ber.*, **56**, 1933 (1923).
[267] Minunni, *Gazz. chim. ital.*, **27**, **II**, 235 (1897).
[268] Stahel, *Ann.*, **258**, 242 (1890).
[269] Ciusa and Rastelli, *Gazz. chim. ital.*, **54**, 72 (1924); *C. A.*, **18**, 2138 (1924).
[270] Barattini, *Gazz. chim. ital.*, **56**, 821 (1926); *C. A.*, **21**, 1251 (1927).
[271] Ragno, *Gazz. chim. ital.*, **75**, 193 (1945); *C. A.*, **41**, 4127 (1947).
[272] Rolla, *Gazz. chim. ital.*, **37**, **I**, 623 (1907).
[273] Braun, *Ber.*, **41**, 2169 (1908).
[274] Hill, *Ber.*, **22**, 607 (1889).
[275] Hill and Jennings, *Am. Chem. J.*, **15**, 158 (1893).
[276] Middendorp, *Rec. trav. chim.*, **38**, 1 (1919).
[277] Landrieu, *Compt. rend.*, **141**, 358 (1905).
[278] Fulda, *Monatsh.*, **23**, 913 (1902).
[279] Bergmann, Ulpts and Witte, *Ber.*, **56**, 679 (1923).
[279a] Hopkins and Williams, Ltd., "Organic Reagents for Organic Analysis," 2nd Ed., p. 70, Brooklyn, Chemical Publishing Co. (1950).
[280a] Minunni, *Gazz. chim. ital.*, **27**, **II**, 232 (1897).

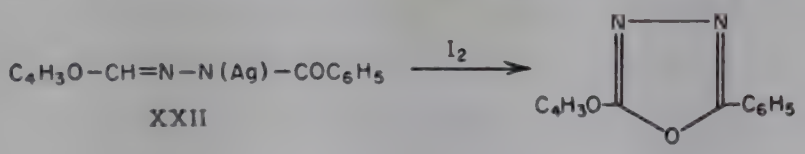
(m.p. 203°) being considered much superior.[279a] Furfurylidenecholylhydrazone, m.p. 143°, is described by Capka.[280] These and a wide variety of other hydrazones derived from furfural and alkyl- and aryl-substituted hydrazines are listed in Table 6. For the products obtained by reacting furfural, 5-methylfurfural and 5-(hydroxymethyl)furfural with 4,6-dinitro-1,3-phenylenedihydrazine and related compounds, see the work of Robert[261] and Vis.[281]

4-Furfurylideneamino-1,2,4-triazole: XXI, m.p. 207° by condensation of furfural with tetrazoline, XIX, under the influence of piperidine.[282] Presumably XIX rearranges to 4-amino-4,1,2-triazole, XX, which may be considered a *sym.*-disubstituted hydrazine.



XIX XX XXI

Acylhydrazines (hydrazides) react similarly with furfural to give the corresponding furfurylidene derivatives, a number of which are listed in Table 7. Thus, benzo(furfurylidenehydrazide) is derived from benzohydrazide. With thiobenzohydrazide and furfural, however, Holmberg[283] obtained indefinite products, although benzaldehyde is converted into the expected crystalline derivative using this reagent. By treatment with iodine, the silver salt, XXII, of benzo(furfurylidenehydrazide) cyclizes with formation of 2-furyl-5-phenyl-1,3,4-oxadiazole, XXIII, m.p. 105°.[284]



XXII XXIII

The difurfurylidene derivative of L-tartaric dihydrazide, $(C_4H_3O—CH=NNH—CO—CHOH)_2$, m.p. 204°, $[\alpha]_D^{20}$ + 220.6°, has been prepared,[285] and Blanksma[286] has described the products obtained by condensing furfural, 5-methylfurfural and 5-(hydroxymethyl)furfural with malonic and succinic dihydrazides and with citric trihydrazide.

[280] Capka, *Chem. Zvesti*, **2**, 1 (1948); *C. A.*, **44**, 1523 (1950).
[281] Vis, *Rec. trav. chim.*, **58**, 387 (1939).
[282] Ruhemann and Merriman, *J. Chem. Soc.*, **87**, 1768 (1905).
[283] Holmberg, *Arkiv. Kemi Mineral. Geol.*, **25**, A, 18 pp. (1947); *C. A.*, **42**, 5918 (1948).
[284] Stollé and Münch, *J. prakt. Chem.*, **70**, 398 (1904).
[285] Frankland and Slator, *J. Chem. Soc.*, **83**, 1349 (1903).
[286] Blanksma and Bakels, *Rec. trav. chim.*, **58**, 497 (1939).

TABLE 7. FURFURAL ACYLHYDRAZONES

Reagent	Furfurylidene derivative, m.p. (°C.)	Ref.
2,4-Dichlorophenoxyacetohydrazide	166–167	287
Benzhydrazide	182	284, 221
o-Hydroxymethylbenzhydrazide	168	286
Chlorobenzhydrazide-*o*	162–163	288
-*m*	184–185	289
-*p*	210–212	290
Bromobenzhydrazide-*o*	162–163	291
-*m*	197–198	292
-*p*	218–219	293
Iodobenzhydrazide-*m*	216	294
-*p*	235 (dec.)	295
Nitrobenzhydrazide-*o*	179–180	296
-*m*	195–197, 197–198	297, 298
-*p*	249–250	299
2-Nitro-4-methylbenzhydrazide	198	300
2-Hydroxymethyl-5-nitrobenzhydrazide	181	286
3,5-Dinitrobenzhydrazide	234–235	301
4-Nitro-3,5-dimethylbenzhydrazide	242–243	302
1-Methyl-3-carbohydrazidopyridinium-*p*-toluenesulfonate	164	303
2-Naphthohydrazide	199–200	304
Cholic hydrazide	145	305
Desoxycholic hydrazide	136	305

[287] Chao, Sah and Oneto, *Rec. trav. chim.*, **68**, 506 (1949).

[288] Sun and Sah, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 359 (1934); *C. A.*, **29**, 466 (1935).

[289] Sah and Wu, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **3**, 443 (1936); *C. A.*, **30**, 8148 (1936).

[290] Shih and Sah, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 353 (1934); *C. A.*, **29**, 466 (1935).

[291] Kao, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **3**, 555 (1936); *C. A.*, **31**, 3825 (1937).

[292] Kao, Tao, Kao and Sah, *J. Chinese Chem. Soc.*, **4**, 69 (1936); *C. A.*, **30**, 8074 (1936).

[293] Wang, Kao, Kao and Sah, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **3**, 279 (1935); *C. A.*, **30**, 2875 (1936).

[294] Sah and Li, *J. Chinese Chem. Soc.*, **14**, 24 (1946); *C. A.*, **43**, 6973 (1949).

[295] Sah and Hsü, *Rec. trav. chim.*, **59**, 349 (1940).

[296] Sah and Kao, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **3**, 461 (1936); *C. A.*, **31**, 3825 (1937).

[297] Meng and Sah, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 347 (1934); *C. A.*, **29**, 465 (1935).

[298] Strain, *J. Am. Chem. Soc.*, **57**, 758 (1935).

[299] Chen, *J. Chinese Chem. Soc.*, **3**, 251 (1935); *C. A.*, **29**, 7229 (1935).

[300] Sah and Wang, *J. Chinese Chem. Soc.*, **14**, 31 (1946); *C. A.*, **43**, 6972 (1949).

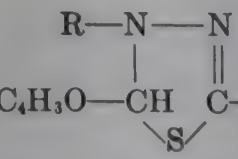
[301] Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 40 (1934); *C. A.*, **28**, 3712 (1934).

[302] Sah and Liu, *J. Chinese Chem. Soc.*, **14**, 94 (1946); *C. A.*, **43**, 6972 (1949).

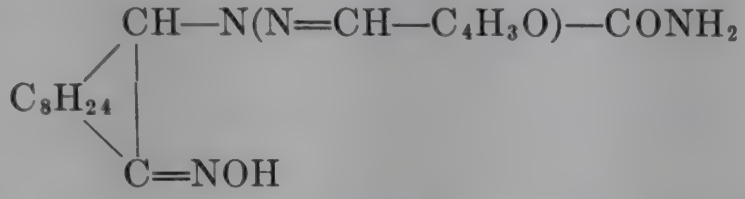
[303] Allen and Gates, *J. Org. Chem.*, **6**, 596 (1941).

[304] Chen and Sah, *J. Chinese Chem. Soc.*, **4**, 62 (1936); *C. A.*, **30**, 8074 (1936).

[305] Vanghelovici, *Bul. Soc. Chim. România*, **20**, **A**, 237 (1938); *C. A.* **34**, 4073 (1940).

2-Furyl-3,5-diphenyl-1,3,4-thiadiazoline:  where R and R′=C_6H_5, m.p. 111–111.5°; from furfural and thiobenzphenylhydrazide, C_6H_5—CS—NHNH—C_6H_5.[306] Where R=*p*-C_6H_4Br and R′=C_6H_5, m.p. 128°; where R=C_6H_5 and R′=α—$C_{10}H_7$, m.p. 118°.[307]

The known furfural semicarbazones and semioxamazones are listed in Tables 8 and 9. In addition to these, the furfurylidene derivative of camphorylsemicarbazide oxime,



m.p. 225° (dec.), has been reported.[308] For a study of the kinetics of the reaction of semicarbazide with furfural, reference should be made to the work of Conant and Bartlett[309] (see also [310, 311, 312]). Absorption characteristics in the ultraviolet and in the visible region are reported by Grammaticakis.[223] Furfural semicarbazone is transformed into the phenylhydrazone when heated with phenylhydrazine in acetic acid[313] (see also [314]). The thiosemicarbazone of furfural has not been reported.

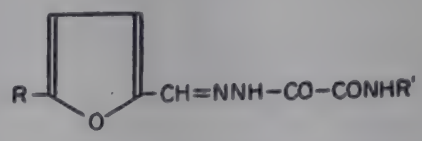
TABLE 8. FURFURAL SEMICARBAZONES

C_4H_3O—CH=NNH—CONHR

Reagent	Derivative		Ref.
	R	M.p. (°C.)	
Semicarbazide	H	202–203, 214–215	313, 217, 314, 223, 279a
4-Phenylsemicarbazide	C_6H_5	185	315, 316
4-*o*-Tolylsemicarbazide	$C_6H_4(CH_3)$	172–175	317
4-*m*-Tolylsemicarbazide	$C_6H_4(CH_3)$	142–143	318
4-*p*-Tolylsemicarbazide	$C_6H_4(CH_3)$	156–157	319
4-(2,4-Dinitrophenyl)semicarbazide	$C_6H_3(NO_2)_2$	227	320
4-(3,5-Dinitrophenyl)semicarbazide	$C_6H_3(NO_2)_2$	225–226	321
4-α-Naphthylsemicarbazide	$C_{10}H_7$	192–193	322
4-β-Naphthylsemicarbazide	$C_{10}H_7$	205–207	323

[306] Wuyts and Wachsmuth, *J. pharm. chim.*, **22**, 289 (1935); *C. A.*, **30**, 3745 (1936).
[307] Wuyts and Lacourt, *Bull. sci. acad. roy. Belg.*, **20**, 156 (1934); *C. A.*, **28**, 3407 (1934).

TABLE 9. SEMIOXAMAZONES OF FURFURAL, 5-METHYLFURFURAL AND 5-(HYDROXYMETHYL)FURFURAL



Reagent	Derivative		M.p. (°C.)	Ref.
	R	R'		
Semioxamazide	H	H	264 (dec.)	324
	$HOCH_2$	H	215, 216	276, 325
5-Methylsemioxamazide	H	CH_3	252–258 (dec.)	326
	$HOCH_2$	CH_3	204–205	326
5-(α-Phenylethyl)semioxamazide	H	$CH_3CH(C_6H_5)$	221–222	327
5-Cyclohexylsemioxamazide	H	C_6H_{11}	263	328
	CH_3	C_6H_{11}	231	328
	$HOCH_2$	C_6H_{11}	226	328
5-Phenylsemioxamazide	H	C_6H_5	258, 259–260	329, 330
	$HOCH_2$	C_6H_5	219	329
5-(2,4-Dimethylphenyl)semioxamazide	H	$(CH_3)_2C_6H_3$	206	331
	CH_3	$(CH_3)_2C_6H_3$	182	331
	$HOCH_2$	$(CH_3)_2C_6H_3$	200	331
5-(2,4,5-Trimethylphenyl)semioxamazide	H	$(CH_3)_3C_6H_2$	228 (dec.)	331
	CH_3	$(CH_3)_3C_6H_2$	180	331
	$HOCH_2$	$(CH_3)_3C_6H_2$	174	331

[308] Forster and Fierz, *J. Chem. Soc.*, **91**, 867 (1907).
[309] Conant and Bartlett, *J. Am. Chem. Soc.*, **54**, 2881 (1932).
[310] Bartlett, *J. Am. Chem. Soc.*, **55**, 741 (1933).
[311] Price and Hammett, *J. Am. Chem. Soc.*, **63**, 2387 (1941).
[312] Sokolov, *Doklady Akad. Nauk S.S.S.R.*, **60**, 825 (1948); *C. A.*, **42**, 8546 (1948).
[313] Knöpfer, *Monatsh.*, **31**, 87 (1910).
[314] Baird and Wilson, *J. Chem. Soc.*, **1926**, 2367.
[315] Grammaticakis, *Bull. soc. chim. France*, **1949**, 410.
[316] Sah and Ma, *J. Chinese Chem. Soc.*, **2**, 32 (1934); *C. A.*, **28**, 3713 (1934).
[317] Lei, Sah and Shih, *J. Chinese Chem. Soc.*, **3**, 246 (1935); *C. A.*, **29**, 7298 (1935).
[318] Sah, Wang and Kao, *J. Chinese Chem. Soc.*, **4**, 187 (1936); *C. A.*, **31**, 655 (1937).
[319] Sah and Lei, *J. Chinese Chem. Soc.*, **2**, 167 (1934); *C. A.*, **29**, 465 (1935).
[320] McVeigh and Rose, *J. Chem. Soc.*, **1945**, 713.
[321] Sah and Tao, *J. Chinese Chem. Soc.*, **4**, 506 (1936); *C. A.*, **31**, 4267 (1937).
[322] Sah and Chiang, *J. Chinese Chem. Soc.*, **4**, 496 (1936); *C. A.*, **31**, 4266 (1937).
[323] Sah and Tao, *J. Chinese Chem. Soc.*, **4**, 501 (1936); *C. A.*, **31**, 4267 (1937).

Several other hydrazine derivatives have been condensed with furfural. Thiocarbohydrazide gives rise to the difurfurylidene derivative, $(C_4H_3O—CH=N—NH)_2CS$, m.p. 250° (dec.).[332] Phenylaminoguanidine is converted into $C_4H_3O—CH=N—N(C_6H_5)—C(NH)NH_2$, m.p. 171° (dec.).[333] Ethylene-1,2-dioxamic acid dihydrazide and furfural give rise to the difurfurylidene derivative, $(—CH_2NH—CO—CONH—N=CH—C_4H_3O)_2$, m.p. >360°[334] (see also [335]).

Furfural Oximes and Related Compounds. When furfural is added to a strongly alkaline solution of hydroxylamine, a mixture of the two stereoisomeric oximes is obtained on subsequent mild acidification with carbon dioxide[336] or ammonium chloride.[337] These may be separated into the α- or *syn* form, m.p. 75–76°, and the β- or *anti* form, m.p. 90–91°, 92°.[337, 338, 339, 340, 340a, 323] In earlier work[336, 341] (see also [342]) the reverse configurations were assigned. The β-oxime is obtainable in high yield by reacting furfural with hydroxylammonium chloride[336, 337, 343] or with sodium hydroxylaminesulfonate.[344] Molecular conductivity measurements[345]; dissociation constants.[346, 347]

α-Furfural oxime is transformed into the β-form by conducting hydrogen chloride through an ethereal solution of the former and decomposing the hydrochloride with sodium carbonate.[336] The same isomerization takes place when the α-oxime is stored in contact with copper, nickel or cobalt chloride.[339] Both forms appear to be stable at room temperature in ethyl

[324] Kerp and Unger, *Ber.*, **30**, 585 (1897).
[325] Erdmann, *Ber.*, **43**, 2391 (1910).
[326] Tierie, *Rec. trav. chim.*, **52**, 357 (1933).
[327] Leonard and Boyer, *J. Org. Chem.*, **15**, 42 (1950).
[328] de Vries, *Rec. trav. chim.*, **61**, 223 (1942).
[329] Tierie, *Rec. trav. chim.*, **52**, 533 (1933).
[330] Sah and Han, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **3**, 469 (1936); *C. A.*, **31**, 3825 (1937).
[331] Van Kleef, *Rec. trav. chim.*, **55**, 765 (1936).
[332] Guha and Dey, *Quart. J. Indian Chem. Soc.*, **2**, 225 (1925).
[333] Pellizzari and Rickards, *Gazz. chim. ital.*, **31**, I, 528 (1901).
[334] Van Alphen, *Rec. trav. chim.*, **53**, 1159 (1934).
[335] Gaade, *Rec. trav. chim.*, **55**, 541 (1936).
[336] Goldschmidt and Zanoli, *Ber.*, **25**, 2573 (1892).
[337] Brady and Goldstein, *J. Chem. Soc.*, **1927**, 1959.
[338] Jordan and Hauser, *J. Am. Chem. Soc.*, **58**, 1304 (1936).
[339] Bryson and Dwyer, *J. Proc. Roy. N. S. Wales*, **74**, 107 (1940).
[340] Raffauf, *J. Am. Chem. Soc.*, **68**, 1765 (1946).
[340a] Calderbank and Le Fèvre, *J. Chem. Soc.*, **1949**, 1462.
[341] Auwers and Ottens, *Ber.*, **57**, 446 (1924).
[342] Yuan and Hua, *J. Chinese Chem. Soc.*, **7**, 76 (1940); *C. A.*, **35**, 5018 (1941).
[343] Odernheimer, *Ber.*, **16**, 2988 (1883).
[344] Semon and Damerell, *J. Am. Chem. Soc.*, **46**, 1290 (1924).
[345] Patwardhan and Deshapande, *J. Indian Chem. Soc.*, **21**, 135 (1944).
[346] Brady and Chokshi, *J. Chem. Soc.*, **1929**, 946.
[347] Brady and Chokshi, *J. Chem. Soc.*, **1929**, 2271.

tartrate, but at 70° each is transformed into an equilibrium mixture comprising approximately 55 per cent of the α- and 45 per cent of the β-form.[348]

Dry distillation of furfural oxime over lead oxide results in dehydration with formation of furonitrile.[349] Heating with strong, aqueous sodium hydroxide also gives rise to the nitrile which is subsequently hydrolyzed to furoic acid. This latter reaction proceeds more readily with the β- (*anti*) oxime than with the α- or *syn* form.[338] The transposition of the oxime to furamide under the influence of Raney nickel is described by Paul.[350, 351] For addition complexes of the oxime with metallic salts, see Bryson and Dwyer[339, 352] and Taylor.[353]

Reduction of the oxime to furfurylamine has been accomplished with sodium amalgam,[354] ammonium amalgam,[355] aluminum amalgam,[356] sodium in alcohol,[357] and catalytically with hydrogen over palladium-charcoal,[358, 359] and Raney nickel.[360, 361]

With phenyl isocyanate, the isomeric furfural oximes give rise to isomeric phenylurethan derivatives, $C_4H_3O—CH=N—O—CONHC_6H_5$ (m.p. 72 and 138°) which decompose to furonitrile and diphenylurea.[336] The related action of phenyl isothiocyanate is reported by Obregia and Gheorghiu.[362]

Methylation of the oximes with methyl sulfate produces mixtures of the O- and N-methyl ethers in the ratio of 0.95 to 1 in the case of the α-oxime, and 0.85 to 1 when the β-oxime is so alkylated[347] (see also [336, 341]).

Furfural oxime benzoate: $C_4H_3O—CH=NO—COC_6H_5$; m.p. 138–138.5°; by treatment of a mixture of α- and β-furfural oximes with benzoyl chloride in ether. In cold hydrochloric acid it is decomposed to furonitrile and benzoic acid[363] (see also [337]).
O-(β-cyanoethyl)furfural oxime: $C_4H_3O—CH=N—OCH_2CH_2CN$; m.p. 116°; from β-furfural oxime and acrylonitrile in dioxane under the influence of sodium methoxide.[364]

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[348] Patterson, Buchanan and Summers, *J. Chem. Soc.*, **1941**, 606.
[349] Borsche, *Ber.*, **39**, 2503 (1906).
[350] Paul, *Bull. soc. chim.* (*5*), **4**, 1115 (1937).
[351] Paul, *Compt. rend.*, **204**, 363 (1937).
[352] Bryson and Dwyer, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 240, 455 (1940).
[353] Taylor, Winckles and Marks, *J. Chem. Soc.*, **1931**, 2778.
[354] Goldschmidt, *Ber.*, **20**, 728 (1887).
[355] Takaki and Ueda, *J. Pharm. Soc. Japan*, **58**, 276 (1938); *C. A.*, **32**, 5376 (1938).
[356] Tseng and Chang, *Science Repts., Natl. Univ. Peking*, **1**, 19 (1936); *C. A.*, **31**, 95 (1937).
[357] Gilman and Hewlett, *Iowa State Coll. J. Sci.*, **4**, 27 (1929).
[358] Williams, *Ber.*, **60**, 2509 (1927).
[359] Williams, *Compt. rend. acad. sci. U.S.S.R.*, **1930, A**, 523; *C. A.*, **25**, 5163 (1931).
[360] Paul, *Bull. soc. chim.* (*5*), **4**, 1121 (1937).
[361] McNally, Dickey and Gray (to Eastman Kodak Co.), U. S. Pat. 2,338,655 (1944); *C. A.*, **38**, 3672 (1944).
[362] Obregia and Gheorghiu, *J. prakt. Chem.*, **128**, 239 (1930).
[363] Minunni and Vassallo, *Gazz. chim. ital.*, **26, I**, 463 (1896).
[364] Bruson and Riener, *J. Am. Chem. Soc.*, **65**, 23 (1943).

Furyl-N-methyl nitrone: $C_4H_3O—CH=\overset{O}{N}—CH_3$; m.p. 91–92°. Obtained by the action of methyl iodide and sodium methoxide on α- or β-furfural oxime in methanol. First formed as a monohydrate, m.p. 56°.[336]

Furyl-N-benzyl nitrone: $C_4H_3O—CH=\overset{O}{N}—CH_2C_6H_5$; m.p. 85, 88°; from β-furfural oxime and benzyl chloride in alcohol with sodium ethoxide.[365, 336] Also prepared by condensation of furfural with benzylhydroxylamine.[365]

Furyl-N-phenyl nitrone: $C_4H_3O—CH=\overset{O}{N}—C_6H_5$; m.p. 91–92°; by condensation of furfural with phenylhydroxylamine.[366]

Furyl-N-*o*-tolyl nitrone: $C_4H_3O—CH=\overset{O}{N}—C_6H_4(CH_3)$-*o*; m.p. 58°.[366]
Furyl-N-*p*-tolyl nitrone: m.p. 119–120°[366] (see also [367]).

Dehydrofurfural oxime: $C_4H_3O—CH=\overset{O}{N}—O—N=CH—C_4H_3O$ (?); by the action of sodium hypochlorite on furfural oxime. Explodes at 130°[368] (see also [369]).

Furyl-N-carbamyl nitrone (?): $C_4H_3O—CH=\overset{O}{N}—CONH_2$; from furfural and isohydroxyurea in ice-water.[370]

From furfural and chloramine, furfurylidenechloroimine has been obtained as an oil of approximately 80 per cent purity, which decomposes instantaneously at 165°.[371] Condensation of the aldehyde with nitramine gives rise to furfurylidenenitrimine, m.p. 117°, although other aldehydes, such as benzaldehyde and thenaldehyde, fail to react with this reagent.[372] Similarly, furfural and aminosulfonic salts give rise to furfurylideneaminosulfonates.[373]

$$C_4H_3O—CHO \xrightarrow{H_2NCl} C_4H_3O—CH=NCl$$
$$C_4H_3O—CHO \xrightarrow{H_2NNO_2} C_4H_3O—CH=NNO_2$$
$$C_4H_3O—CHO \xrightarrow{H_2NSO_3K} C_4H_3O—CH=NSO_3K$$

Miscellaneous Nitrogen Derivatives. On account of its aldehydic character and commercial availability, furfural has been evaluated as a sub-

[365] Werner, *Ber.*, **23**, 2336 (1890).
[366] Ehrhardt, *Ber.*, **30**, 2016 (1897).
[367] Bellavita, *Gazz. chim. ital.*, **70**, 584 (1940); *C. A.*, **35**, 2127 (1941).
[368] Ponzio and Busti, *Gazz. chim. ital.*, **36**, 338 (1906); *C. A.*, **1**, 842 (1907).
[369] Angeli, *Atti accad. Lincei* (*5*), **18, II**, 40 (1909).
[370] Conduché, *Ann. chim phys.* (*8*), **13**, 53 (1908).
[371] Hauser, Gillaspie and LeMaistre, *J. Am. Chem. Soc.*, **57**, 567 (1935).
[372] Suggitt, Myers and Wright, *J. Org. Chem.*, **12**, 373 (1947).
[373] Schroeter, German Pat. 601,105 (1934); *C. A.*, **28**, 7260 (1934).

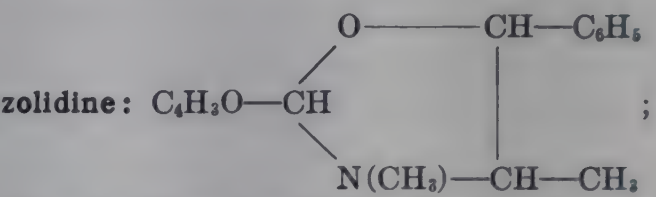
stitute for formaldehyde in numerous applications. Among these are the preparation of furfural-urea and furfural-thiourea resins (see [374, 375, 376]). Similarly, furfural has been compared to formaldehyde as a hardening or tanning agent for protein materials.[377, 378]

Ethyl furfurylidenedicarbamate: $C_4H_3O—CH(NHCOOC_2H_5)_2$; m.p. 169°; from urethan (ethyl carbamate) and furfural under the influence of a little hydrochloric acid.[379]

Benzyl furfurylidenedicarbamate: $C_4H_3O—CH(NHCOOCH_2C_6H_5)_2$; m.p. 163°; from furfural and benzyl carbamate.[380]

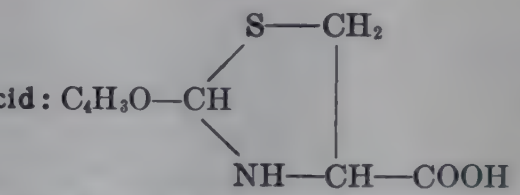
N,N′-furfurylidenediacetamide: $C_4H_3O—CH(NHCOCH_3)_2$; m.p. 187° (dec.). The **dipropionamide,** m.p. 195° (dec.); **dibutyramide,** m.p. 181° (dec.); **dibenzamide,** m.p. 185° (dec.).[381]

2-Furyl-5-phenyl-3,4-dimethyloxazolidine:



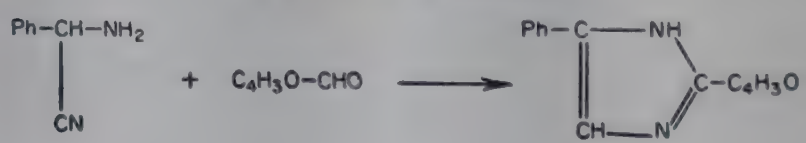
; m.p. 48°; by condensation of furfural with *l*-ephedrine. Useful, in oil solution, as a nasal spray or inhalant[382] (see also [383]).

2-Furyl-4-thiazolidinecarboxylic acid:



; m.p. 125–126°; obtained by condensing furfural with cysteine hydrochloride in aqueous alcohol containing potassium acetate.[384]

2-Furyl-5-phenylimidazole: XXIV, m.p. 132°; by condensation of furfural with α-aminophenylacetonitrile using HCl as a catalyst.[385]



XXIV

[374] Kappeler, British Pat. 293,872 (1927); *C. A.*, **23,** 1729 (1929).

[375] Novotny and Johnson (to John S. Stokes), U. S. Pat. 1,827,824 (1932); *C. A.*, **26,** 862 (1932).

[376] Mangini, *Boll. sci. facoltà chim. ind. Bologna*, **1940,** No. 1–2, 29; *C. A.*, **34,** 3396 (1940).

[377] Brother and McKinney, *Ind. Eng. Chem.*, **30,** 1236 (1938).

[378] Arnold and Quackenbush, *Proc. Iowa Acad. Sci.*, **47,** 231 (1940); *C. A.*, **35,** 7058 (1941).

[379] Bishoff, *Ber.*, **7,** 1078 (1874).

[380] Martell and Herbst, *J. Org. Chem.*, **6,** 878 (1941).

[381] Beaucourt, *Monatsh.*, **49,** 1 (1928).

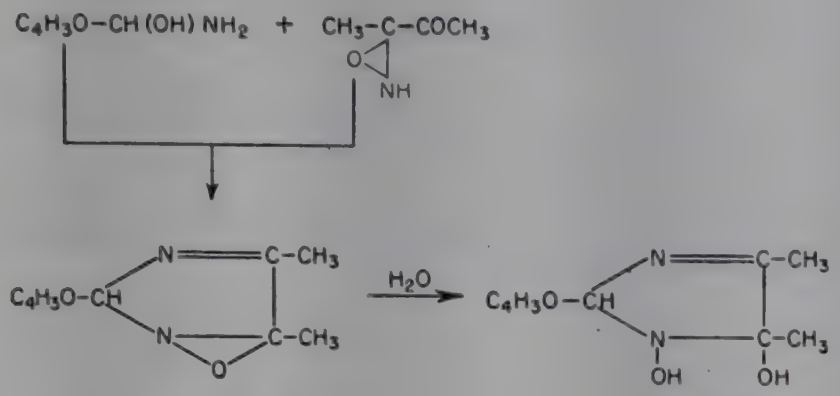
[382] Stuart (to Eli Lilly and Co.), U. S. Pat. 1,749,361 (1930); *C. A.*, **24,** 2243 (1930).

[383] Stratton and Wilson, *J. Chem. Soc.*, **1932,** 1133.

[384] Schubert, *J. Biol. Chem.*, **114,** 341 (1936).

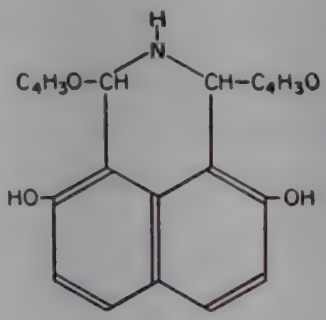
[385] Mironescu, Ioanid and Nicolescu, *Bul. Soc. Chim. România*, **14,** 183 (1933); *Chem. Centr.*, **1933, II,** 875.

2-Furyl-4,5-dimethyl-1,5-epoxyimidazoline (?): XXV, m.p. 170–171°; from furfural and diacetylmonoxime in aqueous ammonia. Forms derivative with phenyl isocyanate, $C_{16}H_{15}O_3N_3$, m.p. 152°. Readily combines with water to give the corresponding 1,5-dihydroxyimidazoline, XXVI, m.p. 112–113°. Diels[386, 387] formulates the reaction as indicated below:

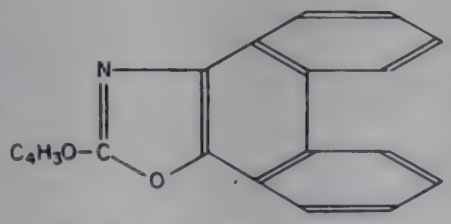


XXV XXVI

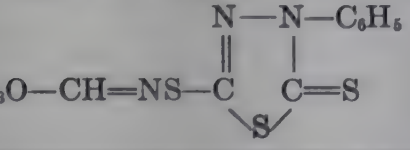
1,8-(1,3-Difuryl-2-azatrimethylene)-2,7-naphthalenediol:



m.p. 198°, from 2,7-naphthalenediol, furfural and alcoholic ammonia. **Triacetate** m.p. 228°; **tribenzoate,** m.p. 211°.[388]

2-Furylphenanthr[9,10-d]oxazole (?):  ; m.p. 231°; by treatment of a mixture of furfural and phenanthraquinone with aqueous ammonia at 100°.[389]

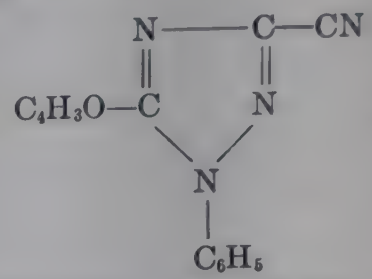
4-Phenyl-5-thio-1,3,4-thiadiazoline-2-sulfenfurfurylideneamide:

 ; m.p. 152°.[390, 391, 123] Treatment with hydrogen

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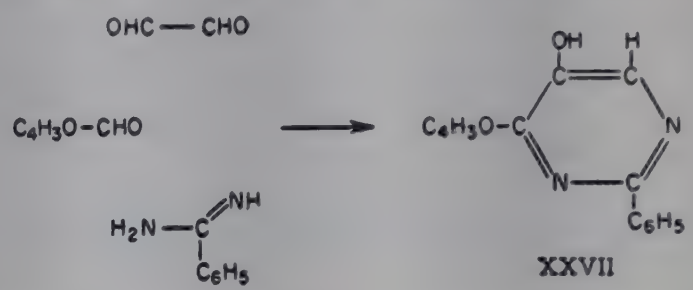
[386] Diels, *Ber.*, **51**, 965 (1918).
[387] Diels and Salomon, *Ber.*, **52**, 43 (1919).
[388] Beschke, Rölle and Strum, *Ann.*, **369**, 157 (1909).
[389] Japp and Wilcock, *J. Chem. Soc.*, **39**, 225 (1881).

chloride in dry ether is reported to give furfurylideneimine hydrochloride, $C_4H_3O—CH=NH\cdot HCl$, m.p. 52°.[390, 391, 123]

1-Phenyl-3-cyano-5-furyl-1,2,4-triazole:  ; m.p. 111°; by

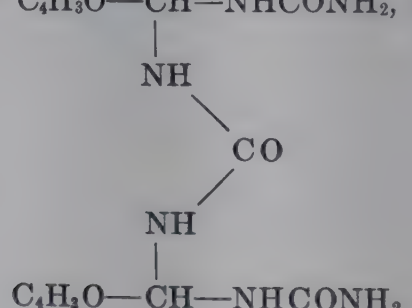
oxidation of $C_4H_3O—CH=N—C(CN)=NNHC_6H_5$, m.p. 146.5°, using ferric chloride.[392]

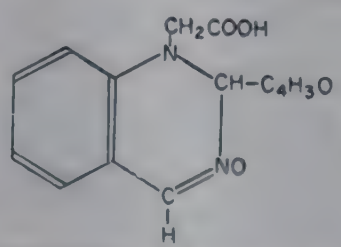
2-Phenyl-4-furyl-5-hydroxypyrimidine: XXVII, m.p. 293.5°; from furfural, benzamidine and glyoxal. The related *p*-tolyl-furyl-hydroxypyrimidine melts at 310°.[393]



XXVII

Bis(furfurylideneamino)tartaric acid (?). Product, a powder derived from tartaric acid (or its nitric ester), ammonia and furfural, was assigned the structure $(C_4H_3O—CH=N—C(OH)COOH)_2$. On heating it decomposes with regeneration of ammonia and other products.[394, 395]

Difurfurylidene-triureide:  heating furfural with an excess of urea.[396]

$C_{14}H_{12}O_4N_2$:  (?); m.p. 195–197° (vigorous dec.); from furfural and *o*-formylphenylglycine (as the oxime).[397]

[390] Wolff, *Ber.*, **29**, 2133 (1898).
[391] Wolff, *J. prakt. Chem.*, **60**, 198 (1899).
[392] Rinman, *Öfversigt af Kongl. (Svenska) Vetenskaps-Akademiens Förhandlingar*, **1897**, 216; Beilstein **XVII**, 279.
[393] Ekeley and Ronzio, *J. Am. Chem. Soc.*, **57**, 1353 (1935).
[394] Maquenne, *Ann. chim. (6)*, **24**, 522 (1891).
[395] Maquenne, *Compt. rend.*, **117**, 740 (1890).
[396] Biginelli, *Gazz. chim. ital.*, **23**, I, 388 (1893).

Sulfur Derivatives

Baumann and Fromm[398] passed hydrogen sulfide into a cold alcoholic solution of furfural containing hydrochloric acid and obtained a mixture of the α- and β-forms of trimeric thiofurfural,[e] $(C_4H_3O—CHS)_3$, melting at 128 and 229° (dec.), respectively. Treatment with iodine in ethyl iodide transforms the α- into the β-isomer. A higher polymeric thiofurfural, m.p. 95–98° (softens at 80°) is also known.[399, 121, 400, 398, 401, 115] On slow distillation, these products decompose with formation of *sym.*-difurylethylene, $C_4H_3O—CH=CH—C_4H_3O$.[400, 398, 402] The value of the polymeric thiofurfurals as rubber accelerators is discussed by Trickey and Leuck[403], and Vignos[404] has patented their use as corrosion inhibitors.

With ammonium polysulfide, furfural gives rise to dithiofuroic acid (p. 527). For plastic products obtained by the action of alkaline polysulfides, see Patrick.[405] Soluble, black dyes produced from furfural and a polysulfide, are discussed by Darling[406] and Mangini[407] (see also [408]).

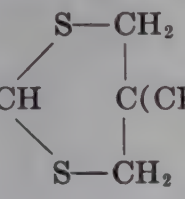
Furfuryl disulfide, $(C_4H_3O—CH_2S)_2$, is derived from furfural by the action of alkali or ammonium hydrosulfides (see p. 249).

For the reaction of furfural with ammonium trithiocarbonate, see Levi.[409]

Furfural *p*-nitrobenzyl mercaptal: $C_4H_3O—CH(SCH_2C_6H_4NO_2)_2$; m.p. 87°.[410]

Furfural 2-carboxyethyl mercaptal: $C_4H_3O—CH(SCH_2CH_2COOH)_2$; m.p. 87–88°.[411]

Furfural 2,2-dimethyltrimethylene mercaptal:



m.p. 62–63.5°.[412]

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[e] A selenofurfural is also reported[115] but no constants are given.

[398] Gluud, *Ber.*, **48**, 425 (1915).

[398] Baumann and Fromm, *Ber.*, **24**, 3591 (1891).

[399] Meints and Wilkinson, *J. Am. Chem. Soc.*, **51**, 803 (1929).

[400] Bruins, *J. Am. Chem. Soc.*, **51**, 1270 (1929).

[401] Lintner, *Z. ges. Brauw.*, **33**, 361 (1910); *C. A.*, **5**, 755 (1911).

[402] Schwanert, *Ann.*, **134**, 61 (1865).

[403] Trickey and Leuck, *Ind. Eng. Chem.*, **18**, 812 (1926).

[404] Vignos (to Rubber Service Laboratories), U. S. Pat. 1,843,653 (1932); *C. A.*, **26**, 1567 (1932).

[405] Patrick, U. S. Pat. 1,996,487 (1935); *C. A.* **29**, 3421 (1935).

[406] Darling, *Textile Am.*, **37**, 17, 25 (1922); *C. A.*, **16**, 1321 (1922).

[407] Mangini, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 169; *C. A.*, **37**, 533 (1943).

[408] Monroe, *Ind. Eng. Chem.*, **13**, 133 (1921).

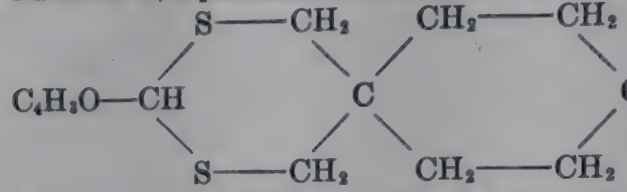
[409] Levi, *Gazz. chim. ital.*, **61**, 673 (1931); *C. A.*, **26**, 1251 (1932).

[410] Schaeffer and Muria, *Ber.*, **40**, 2007 (1907).

[411] Holmberg, *Arkiv Kemi Mineral. Geol.*, **15, A**, 1 (1942); *C A.*, **37**, 85 (1943).

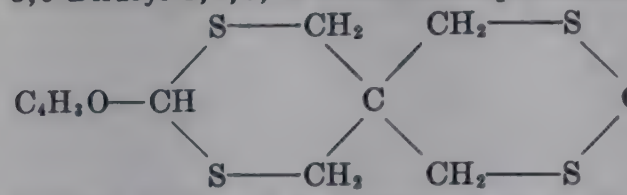
[412] Backer and Tamsma, *Rec. trav. chim.*, **57**, 1183 (1938).

Furfural 2,2-pentamethylenetrimethylene mercaptal:



; m.p. 103°.[412]

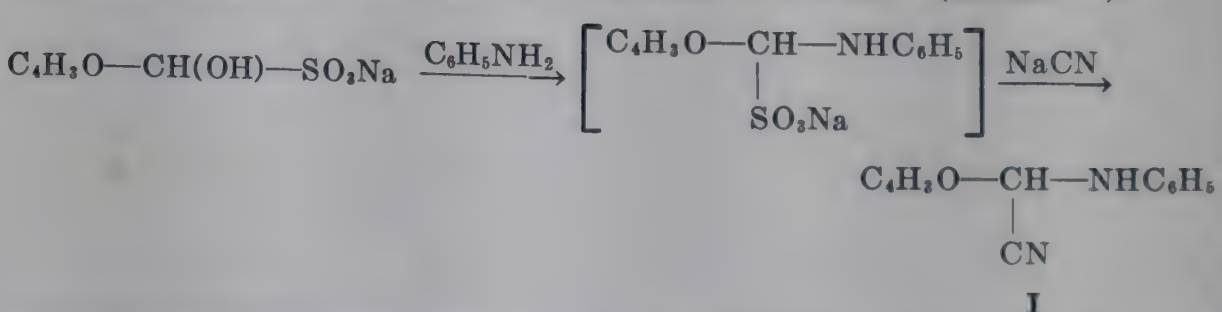
3,9-Difuryl-2,4,8,10-tetrathia-6-spiroundecane:



; m.p. 132.5–133°. This spirocyclic mercaptal was prepared as an identification derivative by reacting furfural with tetrakis(mercaptomethyl)methane.[413]

Furfural 3-thienyl mercaptal: $C_4H_3O—CH(S—C_4H_3S)_2$; no constants. Prepared from furfural and 3-thiophenethiol under the influence of anhydrous HCl. Reported to be effective as an antioxidant and corrosion inhibitor for lubricating oils.[413a]

Furfural sodium bisulfite: $C_4H_3O—CH(OH)—SO_3Na$; from furfural and aqueous sodium bisulfite.[414] The yield from equimolecular quantities of reactants in a single preparation is generally low due to the high solubility of the addition compound in the aqueous medium. Subsequent preparations utilizing the mother liquor are productive of almost quantitative yields.[105] For a study of the dissociation of furfural sodium bisulfite in aqueous solution, see Kerp and Wohler[415] and Höpner.[416] Its toxicity is discussed by Gibbs and Reichert.[417] Reaction with cold, aqueous sodium cyanide separates a light colored oil (furfural cyanohydrin?) which rapidly darkens and resinifies to a tarry, greenish-black mass.[105] Condensation with aniline and subsequent treatment with sodium cyanide produces, in high yield, a bronze-colored crystalline product believed to be α-furyl-α-anilinoacetonitrile, I.[105] The corresponding product obtained by reacting morpholine in place of aniline is an orange-colored oil, b.p. 137-138° (3 mm.); d^{25} 1.1564; n_D^{25} 1.5076.[105] A related product, m.p. 153°, is apparently obtained by passing sulfur dioxide into an alcoholic solution of ethylenediamine and subsequently adding this solution to furfural[418] (see also [419]).



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[413] Backer and Evenhuis, *Rec. trav. chim.*, **56**, 681 (1937).

[413a] Brooks (to Socony-Vacuum Oil Co.), U. S. Pat. 2,480,831 (1949); *C. A.*, **44**, 321 (1950).

[414] Schwanert, *Ann.*, **114**, 63 (1860); **116**, 257 (1861).

[415] Kerp and Wohler, *Arb. kais. Gesundh.*, **32**, 120 (1909); *Chem. Centr.*, **1909**, II, 710.

[416] Höpner, *Das Papier*, **1**, 102 (1947); *C. A.*, **42**, 3701 (1948).

[417] Gibbs and Reichert, *Am. Chem. J.*, **13**, 361 (1891).

[418] Michaelis and Graentz, *Ber.*, **30**, 1009 (1897).

[419] Knoevenagel, *Ber.*, **37**, 4073 (1904).

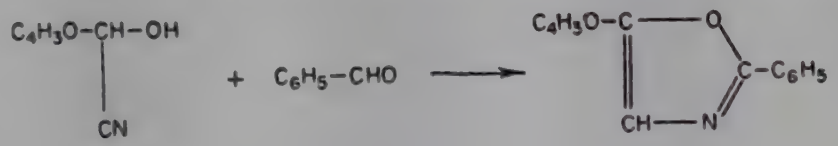
Reduction of furfural sodium bisulfite with zinc dust in acetic acid is reported to produce sodium furfuralsulfoxylate, $C_4H_3O—CH(OH)—OSONa$, in 85 per cent yield.[420]

Furfural Cyanohydrin

The benzoyl derivative (m.p. 48–49°) of furfural cyanohydrin has been isolated in high yield by the action of benzoyl chloride and alkali cyanide on furfural.[421, 422, 423, 424]

$$C_4H_3O—CHO \xrightarrow[C_6H_5—COCl]{NaCN} C_4H_3O—CH(O—CO—C_6H_5)—CN$$

The acetate has likewise been described, a liquid boiling at 91–93° (3 mm.); d_{24} 1.175.[425] The free cyanohydrin, however, has not been described, although Degering and Boatright[425a] (see also [385]) report its formation from furfural and dry hydrogen cyanide in the presence of potassium carbonate. In chloroform solution, the cyanohydrin reacts with benzaldehyde under the influence of hydrogen chloride to produce 2-phenyl-5-furyloxazole, I, m.p. 216°.[385] The isomeric 2-furyl-5-phenyloxazole, m.p. 212,° is similarly derived from furfural and benzaldehyde cyanohydrin; 2-furyl-5-*p*-anisyloxazole, m.p. 220°, from furfural and anisaldehyde cyanohydrin.[385] Other



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reactions of furfural cyanohydrin in solution are reported elsewhere; see [426, 427].

Cannizzaro Reaction

This reaction of furfural was first reported by Ulrich in 1861,[428] who treated the aldehyde with alcoholic potassium hydroxide and successfully

[420] Porai-Koshitz and Itenberg, *J. Applied Chem. U.S.S.R.*, **5**, 761 (1932); *C. A.*, **27**, 290 (1933).

[421] Aloy and Rabaut, *Bull. soc. chim.* (*4*), **13**, 457 (1913).

[422] Green, *J. Chem. Soc.*, **1926**, 328.

[423] Lukeš, Kastner, Gut and Herben, *Collection Czechoslov. Chem. Communs.*, **12**, 647 (1947); *C. A.*, **42**, 5852 (1948).

[424] Normant, *Compt. rend.*, **225**, 580 (1947).

[425] Hansley and Bristol (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,456,188 (1948); *C. A.*, **43**, 2631 (1949).

[425a] Degering and Boatright, *J. Am. Chem. Soc.*, **72**, 5137 (1950).

[426] Matheson and Blaikie, British Pat. 264,143 (1926); *C. A.*, **22**, 91 (1928).

[427] Asahina and Teresaka, *J. Pharm. Soc. Japan*, **494**, 19 (1923); *Chem. Centr.*, **1923**, III, 434.

[428] Ulrich, *Chem. News*, **3**, 116 (1861).

isolated potassium furoate. He correctly assumed the simultaneous formation of furfuryl alcohol as an additional product, although he did not attempt its recovery at that time.

$$2\ C_4H_3O{-}CHO + OH^- \rightarrow C_4H_3O{-}CH_2OH + C_4H_3O{-}COO^-$$

Since then, the Cannizzaro reaction has been employed extensively for the laboratory preparation of the alcohol and/or acid (see [429, 430, 109, 431, 432, 275, 433, 110, 434]); and Gilman and Selby[435] have reported on the optimum conditions for recovery of the products when the dismutation of the aldehyde is carried out using methanolic sodium hydroxide. In his procedure involving the conversion of comparatively large quantities of furfural, Wilson[436] employs an excess of strong aqueous sodium hydroxide (see also [437, 438]), and recommends that the reaction temperature be maintained below 20°. Following this method, Hurd[439] (see also [440]) demonstrated that the excess alkali was desirable from the standpoint of the yield of furoic acid, but that it interfered with the recovery of furfuryl alcohol by distillation. This difficulty was overcome by prior neutralization of the excess base with furoic acid or with ammonium sulfate. High yields of the alcohol and acid are reported by Kasiwagi[441] on heating furfural, in toluene, with an equimolecular quantity of sodamide and subsequently adding water. For the dismutation of furfural by means of yeast, see Neuberg, Lustig and Dresel,[442] and Euler and Grabe.[443]

The mechanism of the Cannizzaro reaction, with particular reference to furfural, was studied by Geib[444] who obtained data indicating that in homogeneous aqueous or aqueous–alcoholic solution, the reaction is of the fourth order.

$$-\frac{dF}{dt} = k[F]^2[OH^-]^2, \text{ where } F = \text{concentration of furfural}$$

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[429] Limpricht, *Ann.*, **165**, 253 (1873).
[430] Hill, *Am. Chem. J.*, **3**, 33 (1881).
[431] Schiff, *Ann.*, **261**, 254 (1891).
[432] Wissell and Tollens, *Ann.*, **272**, 291 (1893).
[433] Gennari, *Gazz. chim. ital.*, **24**, I, 246 (1894).
[434] André, *Compt. rend.*, **128**, 1035 (1899).
[435] Gilman and Selby, *Iowa State Coll. J. Sci.*, **5**, 15 (1930).
[436] Wilson, "Organic Syntheses," Collective Vol. I, p. 269, New York, John Wiley and Sons (1932).
[437] Erdmann, *Ber.*, **35**, 1855 (1902).
[438] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).
[439] Hurd, Garrett and Osborne, *J. Am. Chem. Soc.*, **55**, 1082 (1933).
[440] Katsuno, *J. Soc. Chem. Ind. Japan*, **46**, 1028 (1943); *C. A.*, **42**, 7285 (1948).
[441] Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 66 (1926); *C. A.*, **20**, 2491 (1926).
[442] Neuberg, Lustig and Dresel, *Arch. Biochem.*, **19**, 163 (1948).
[443] Euler and Grabe, *Archiv. Kemi, Mineral. Geol.*, **9**, No. 50, 6 pp. (1928); *C. A.*, **22**, 2574 (1928).
[444] Geib, *Z. physik. Chem.*, *A*, **169**, 41 (1934); *C. A.*, **28**, 5742 (1934).

He reports the temperature coefficient to be approximately 1.9 per 10°, corresponding to an activation energy of 11 kcal. The velocity is practically identical for sodium or potassium hydroxides, and in 60 per cent alcohol is about one-fifth of that in aqueous medium.

More recently, Eitel[445] extended Geib's work to systems of widely varying concentration of reactants: from a sixty-fold excess of sodium hydroxide to a twelve-fold excess of furfural. In the latter instance, he observed a third order phenomenon, that the velocity is proportional to the square of the furfural concentration, but only directly proportional to the concentration of hydroxyl ion. Deviations from both third and fourth order rate constants were found in systems containing a large excess of hydroxyl ion. Eitel concluded that the Cannizzaro reaction obeys a complicated rate law which in special cases degenerates to a trimolecular limiting law (see also [446]).

Geib[444] found that the inclusion of oxidizing agents (peroxides, etc.) failed to affect either the course or the rate of reaction, although it has been demonstrated in later work[447] that the dismutation of 5-bromofurfural is markedly accelerated by addition of a trace of hydrogen peroxide. The effect of catalytic metals has not received much attention, although Ashida and Bebeko[448] have found Raney nickel to promote the reaction. Recently, however, it has been found[105] that even traces of metallic silver produce a tremendous acceleration of the dismutation in aqueous sodium hydroxide. On the other hand, it is of interest to note that this catalytic effect of silver is completely eliminated if oxygen is excluded, as by purging the system continuously with nitrogen.[105]

A secondary reaction usually accompanies the Cannizzaro reaction of furfural. The product of this competitive reaction is a dark brown, alkali-soluble, resinous material, the identity of which is unknown at this time. The rate of formation of the resin is considerably lower than the rate of dismutation of the aldehyde, hence from the standpoint of quantity, the resin is generally a relatively minor impurity in the products of the Cannizzaro reaction. The high tinctorial power of the resin imparts a very dark color to the reaction medium, however; and this can be troublesome in connection with the recovery of high quality furfuryl alcohol and furoic acid. The difficulty can be almost entirely eliminated by accelerating the Cannizzaro reaction in aqueous alkali by addition of a small quantity of silver. The formation of resin is not catalyzed by silver, and under these conditions the extent of the competing reaction becomes negligible.[105]

Except for a brief period during the early industrial development of

[445] Eitel, *Monatsh.*, **74**, 124 (1942).
[446] Alexander, *J. Am. Chem. Soc.*, **69**, 289 (1947).
[447] Chute, Orchard and Wright, *J. Org. Chem.*, **6**, 157 (1941).
[448] Ashida and Bebeko, *J. Agr. Chem. Soc. Japan*, **23**, 174 (1949); *C. A.*, **44**, 7781 (1950).

furfural, the production of furfuryl alcohol and furoic acid by the Cannizzaro reaction has not received much attention from a commercial standpoint. This is due to the fact that these products can be produced directly from the aldehyde in high yield by catalytic reduction and oxidation, respectively. However, a novel application of the reaction was developed some years ago dealing with the manufacture of a "brightening" agent for addition to cadmium plating solutions,[449] and Trickey and Miner[450] patented a procedure for the simultaneous production of furoic acid and resinous bodies from furfural by appropriately working up the products of the Cannizzaro reaction. More recently, Hadnagy[451] has employed this reaction of furfural as a step in the production of synthetic detergents.

A "crossed" Cannizzaro reaction involving furfural was first reported by Rodionov and Fedorova.[452] This general method for the reduction of aromatic aldehydes by treatment with formaldehyde and alkali was again applied to furfural by Berkenheim and Dankova[453] (see also [454]) who were able to isolate furfuryl alcohol in 90 per cent yield based on the following equation.

$$C_4H_3O{-}CHO + HCHO + NaOH \rightarrow C_4H_3O{-}CH_2OH + HCOONa$$

When a mixture of furfural and benzaldehyde was treated with aqueous alkali, analysis of the products revealed that furfural is oxidized to a greater extent than benzaldehyde; ratio *ca.* 5:3.[455] Thus, the molar ratio of furfuryl alcohol to benzyl alcohol was found to be 0.56:1; of benzoic acid to furoic acid, 0.63:1, showing that the disproportionation is measurably in favor of the reduction of benzaldehyde.

Under anhydrous conditions, treatment of furfural with sodium furfuroxide produces furfuryl furoate in good yield.[456] For the related dismutation of the aldehyde under the influence of aluminum or magnesium alkoxides, see Child and Adkins[457] and Nakai.[458]

[449] Hogaboom and Diggin (to Hanson-Van Winkle-Munning Co.), U. S. Pat. 1,893,368 (1933); *C. A.*, **27**, 2101 (1933).

[450] Trickey and Miner (to The Quaker Oats Co.), U. S. Pat. 1,665,236 (1928); *C. A.*, **22**, 1783 (1928).

[451] Hadnagy, Italian Pat. 392,519 (1942).

[452] Rodionov and Fedorova, *J. Gen. Chem. U.S.S.R.*, **7**, 947 (1937); *C. A.*, **31**, 5338 (1937).

[453] Berkenheim and Dankova, *J. Gen. Chem. U.S.S.R.*, **9**, 924 (1939); *C. A.*, **34**, 368 (1940).

[454] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 19 (1942); *C. A.*, **44**, 8859 (1950).

[455] Hazlet and Callison, *J. Am. Chem. Soc.*, **66**, 1248 (1944).

[456] Nielsen, *J. Am. Chem. Soc.*, **66**, 1230 (1944).

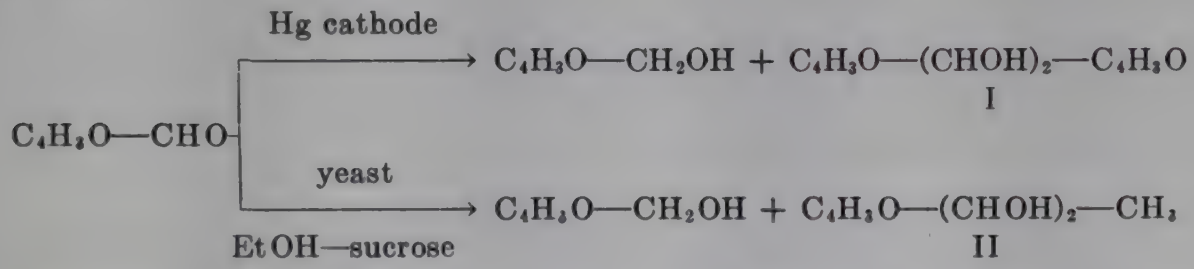
[457] Child and Adkins, *J. Am. Chem. Soc.*, **47**, 798 (1925).

[458] Nakai, *Biochem. Z.*, **152**, 258 (1924); *C. A.*, **19**, 2807 (1925).

Reduction

Schmelz and Beilstein[459] (see also [460]) attempted reduction of furfural using sodium amalgam. Some furfuryl alcohol was obtained, but inasmuch as sodium furoate was also a product, it would appear that, at least to some extent, the aldehyde underwent dismutation by the Cannizzaro reaction. Interaction of furfural and disodium-tetraphenylethane results in the formation of a mixture of *sym.*-tetraphenylethylene, furfuryl alcohol and sodium furoate.[23]

Electrolytic reduction,[f] using a lead or mercury cathode in approximately neutral solution, gives rise to furfuryl alcohol accompanied by the two stereoisomeric pinacols (hydrofuroins, I) in a maximum yield of 63 per cent, and some resin[463] (see also [464]). A similar result was reported by Lintner and Liebig[465, 466] who effected enzymatic reduction of the aldehyde by the action of fermenting yeast (see also [442]). Two products were isolated, furfuryl alcohol and a compound which was later[467] formulated as 1-furyl-1,2-propanediol, II, on the basis of its cleavage to furfural and acetaldehyde by the action of lead tetracetate. Presumably II has its origin in the mixed acyloin, 1-furyl-1-hydroxy-2-propanone, $C_4H_3O—CHOH—COCH_3$, produced from furfural and acetaldehyde formed during the course of reaction (see [468]).



Hydrofuroin: (*sym.*-difurylethyleneglycol); I. In admixture with isohydrofuroin, boiling in the range 130–135° (1 mm.), and melting at 61–62°. **Diacetate,** two forms, m.p. 112–113 and 67–68°, respectively. **Dibenzoate,** two forms, m.p. 180 and 99–100°, respectively [463] (see also [469]).

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[f] The electrolytic reduction potential of furfural was measured by Tati[461] (see also [462]) who observed that the saturation current varied with pH, reaching a maximum at pH 8.0.

[459] Schmelz and Beilstein, *Ann. suppl.*, **3**, 275 (1864).
[460] Baeyer, *Ber.*, **10**, 355 (1877).
[461] Tati, *J. Agr. Chem. Soc. Japan*, **14**, 1371 (1938); *C. A.*, **33**, 7669 (1939).
[462] Bonino and Scaramelli, *Ber.*, **75**, 1948 (1942).
[463] Albert and Lowy, *Trans. Electrochem. Soc.*, **75**, 367 (1939).
[464] Law, *J. Chem. Soc.*, **89**, 1512 (1906).
[465] Lintner and Liebig, *Z. physiol. Chem.*, **72**, 449 (1911); *C. A.*, **5**, 3297 (1911).
[466] Lintner and Liebig, *Z. physiol. Chem.*, **88**, 109 (1913); *C. A.*, **8**, 1126 (1914).
[467] Liang, *Z. physiol. Chem.*, **244**, 238 (1936); *C. A.*, **31**, 1066 (1937).
[468] Hildebrandt and Klavehn (Knoll A.-G. chem. Fab.), German Pat. 585,667 (1933); *C. A.*, **28**, 1355 (1934).
[469] Neuberg, Lustig and Cagan, *Arch. Biochem.*, **1**, 391 (1943).

1-Furyl-1,2-propanediol: II; m.p. 50.5°; b.p. 127–130° (11 mm.); $[\alpha]_D$ − 10.5°. **Diacetate,** b.p. 246–248° (720 mm.); **bis-*p*-nitrobenzoate,** m.p. 150–151°; **bisphenylurethan,** m.p. 195°. The isopropylidene derivative, b.p. 194.5° (712 mm.); d_4^{17} 1.0525; n_D^{17} 1.4598, was obtained by treating II with acetone in the presence of phosphorus pentoxide.[467, 465, 466]

When a mixture of furfural and an α,β-unsaturated aldehyde is reduced by a zinc-copper couple in acetic acid, unsaturated glycols, III and IV, are produced. Under the same conditions, furfural alone gives only resinous products and a little furfuryl alcohol.[470, 471]

$$C_4H_3O{-}CHO + RCH{=}CHCHO \xrightarrow[AcOH]{Zn{-}Cu} C_4H_3O{-}CH(OH)CH(OH)CH{=}CHR + [RCH{=}CHCH(OH)]_2$$

III IV

1-Furyl-3-buten-1,2-diol: III (R = H); a mixture of the two racemic isomers, b.p. 115–116° (3 mm.); d_4^{21} 1.1612; n_D^{17} 1.5130. With phenyl isocyanate, two **phenylurethans** are obtained, m.p. 189° and 116–118°, respectively. The mixed diols are obtained in 40 per cent yield together with IV (R = H) (15 per cent yield) by reduction of a mixture of furfural and acrolein according to the scheme illustrated above.[470, 471]

1-Furyl-3-penten-1,2-diol: III (R = CH_3); isomeric mixture, b.p. 125° (2 mm.); d_4^{20} 1.1322; n_D^{20} 1.5120, giving rise to two **phenylurethans,** one of which melts at 222–223°, and the other very much lower (no m.p. given). The mixed diols were obtained (15 per cent yield) along with IV (R = CH_3) (10 per cent yield) from furfural and crotonaldehyde as indicated above.[470, 471]

Reduction of the carbonyl group is also achieved by the Meerwein-Ponndorf-Verley reaction. Thus, treatment of furfural with aluminum ethoxide in alcohol gives rise to furfuryl alcohol in 88 per cent yield[472]; aluminum isopropoxide in isopropyl alcohol produces the alcohol in 75 per cent yield.[473] The action of butoxymagnesium iodide is similar, but less rapid (10 per cent conversion in four days), with formation of furfuryl alcohol and furfurylidenebutyraldehyde.[474] Shankland and Gomberg[475] employed the iodomagnesium derivative of hydrobenzoin, and isolated furfuryl alcohol in 59 per cent yield.

By the Wolff-Kizhner technique, basic decomposition of the hydrazone,

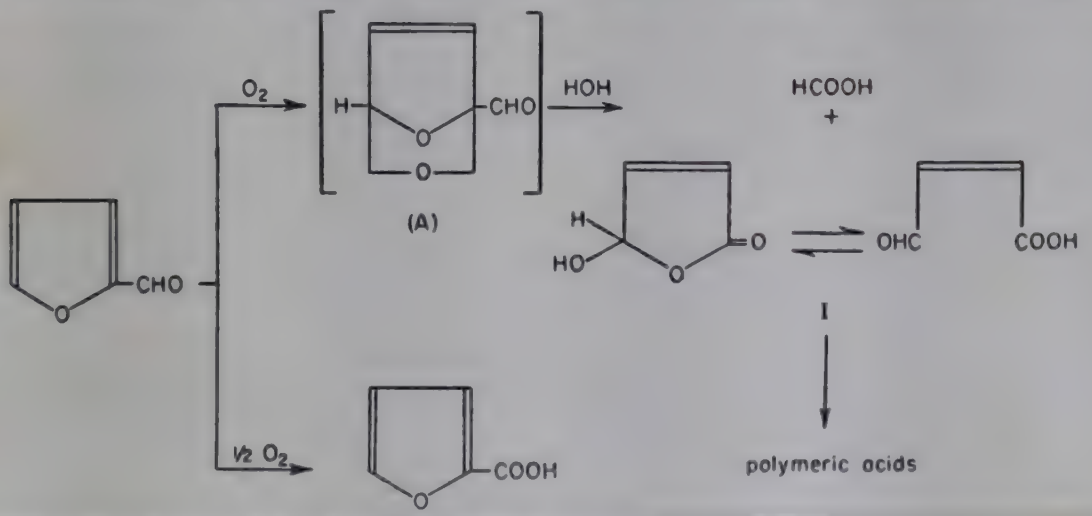
[470] Wiemann, *Compt. rend.*, **198,** 2263 (1934).
[471] Wiemann, *Bull. soc. chim.* (*5*), **2,** 1209 (1935).
[472] Meerwein and Schmidt, *Ann.*, **444,** 221 (1925).
[473] Adams, "Organic Reactions," Vol. II, p. 207, New York, John Wiley and Sons (1944).
[474] Grignard and Fluchaire, *Ann. chim.*, **9,** 5 (1928).
[475] Shankland and Gomberg, *J. Am. Chem. Soc.*, **52,** 4973 (1930).

furfural is reduced to methylfuran,[476] (see also [477, 219, 217, 478]). The Clemmenson method as applied to furfural failed to give methylfuran.[479]

For the catalytic hydrogenation of furfural, see Chapter 15.

Oxidation

For a long time it has been known that furfural discolors on standing with simultaneous formation of acidic products. More recently it has been demonstrated that these changes are the result of autoxidation, the course of which has been found to be quite complex. Whereas benzaldehyde is rapidly and completely converted into benzoic acid by way of perbenzoic acid, the amount of furoic acid obtained from furfural on exposure to air (or oxygen) is only about one-tenth of that calculated on the basis of the oxygen consumed. In other words, furfural behaves only to a limited extent, as does benzaldehyde, and probably by a similar mechanism. However, the chief products of autoxidation of the furan aldehyde are formic acid and complex polymeric acids derived from β-formylacrylic acid, I, which is, in part, isolable in the monomeric form. Furoic acid can not be the precursor of these products, since it is notably stable in storage, and would, in any event, give rise to carbon dioxide, not formic acid, on oxidative degradation. It is concluded, therefore, that the major point of initial attack by oxygen on furfural is the nucleus rather than the formyl group. A mechanism has been formulated[480] which predicts the formation of A, an ozonide, as the key intermediate, although it is recognized that this is probably an oversimplification (see also [481, 482, 99, 483]). The available information is insufficient to permit a complete kinetic analysis of the reaction. It might be



[476] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).
[477] Gilman and Wright, *J. Am. Chem. Soc.*, **54**, 4108 (1932).
[478] Zelinskii and Shuikin, *Compt. rend. acad. sci. U.R.S.S., N.S.*, **1933**, 60; *C. A.*, **28**, 2002 (1934).
[479] Gilman and Vernon, *J. Am. Chem. Soc.*, **46**, 2576 (1924).
[480] Dunlop, Stout and Swadesh, *Ind. Eng. Chem.*, **38**, 705 (1946).
[481] Schenck, *Naturwissenschaften*, **31**, 387 (1943); *C. A.*, **38**, 2336 (1944).
[482] Schenck, *Ber.*, **77**, 661 (1944).
[483] Clauson-Kaas and Fakstorp, *Acta Chem. Scand.*, **1**, 415 (1947).

thought that perfuroic acid (furoyl hydrogen peroxide, see p. 525) is the vital intermediate; and that perfuroic acid attacks unchanged furfural to produce I (above) and formic acid, being itself reduced to furoic acid in the process. However, such a postulate requires that formic and furoic acids be found in the reaction mixture in equimolecular proportions, whereas the isolable furan acid is always much less than this.[g, 480] This is not to say that peracids, if present, cannot function in this manner. Indeed, Boeseken[485] has demonstrated that peracetic acid reacts with furfural[h] to produce almost the stoichiometric quantity of formic acid, along with some I (above), maleic acid, and resinous material which he did not characterize. Here again, the nucleus is almost exclusively the point of initial attack, since if furoic acid were an intermediate, carbon dioxide would have been produced, not formic acid.

Iron acts as a pro-oxidant, greatly accelerating the rate of acid formation in furfural on exposure to air.[16] Tin and aluminum are much less pro-oxidant,[16] and cobalt is reported to be antioxidant in its action.[487] It is important to observe, however, that the autoxidation of furfural is subject to autoinhibition, and practically ceases when about 7–8 per cent of the available aldehyde has been destroyed. Furthermore, the addition of water has been found to materially decrease the rate of absorption of oxygen,[i, 480] and a similar result has been obtained by addition of small amounts of organic bases, preferably tertiary amines, or of the common phenolic anti-oxidants[480, 16] (see also [489, 490]). Other inhibitors (see also [491, 492, 493]) which

[g] Additional indirect evidence that comparatively little perfuroic acid is formed on autoxidation of furfural is seen in the work of Swern.[484] He found that the epoxidation of ethylenic double bonds, as by passing air through a solution of oleic acid and benzaldehyde, proceeds readily, and in high yield, by way of perbenzoic acid. He further called attention to the fact that furfural cannot be successfully substituted for benzaldehyde in this reaction.

[h] By contrast, peracetic acid oxidizes benzaldehyde almost quantitatively to benzoic acid.[486]

[i] In his study of the antioxygenic properties of the sterols, Montignie[488] found that the addition of cholesterol or ergosterol to furfural failed to affect the rate of oxygen absorption.

[484] Swern, Findley and Scanlan, *J. Am. Chem. Soc.*, **66**, 1925 (1944).

[485] Boeseken, Vermij, Bunge and van Neeuwen, *Rec. trav. chim.*, **50**, 1023 (1931).

[486] D'Ans and Kneip, *Ber.*, **48**, 1136 (1915).

[487] Dufraisse and Nakae, *Compt. rend.*, **194**, 880 (1932).

[488] Montignie, *Bull. soc. chim.*, **45**, 709 (1929).

[489] Moureu and Dufraisse, *Chemistry and Industry*, **47**, 819 (1928).

[490] Imoto and Kawata, *J. Soc. Chem. Ind. Japan*, **46**, 457 (1943); *C. A.*, **42**, 6803 (1948).

[491] Moureu, Dufraisse and Badoche, *Compt. rend.*, **186**, 1673 (1928); **187**, 157, 917, 1092 (1928).

[492] Moureu, Dufraisse and Laplagne, *Compt. rend.*, **187**, 1266 (1928).

[493] Dufraisse and Horclois, *Compt. rend.*, **191**, 1126 (1930).

have been reported include alkyl sulfides,[494] sodium hydrosulfite,[495] hydrofuramide[496] and butyramide.[497] The function of the inhibitors is apparently to retard initiation of the oxidation; they provide a more or less extended induction period when furfural is exposed to air at ordinary temperatures. When this induction period is over, the inhibitor has no further action and autoxidation ensues. At elevated temperatures (150–200°), if a similar induction period exists, it is of extremely short duration, and under such conditions tertiary amines and phenolic antioxidants are of little or no value.[105] The only manner of preventing autoxidation of furfural at high temperature is to provide an inert atmosphere, such as nitrogen or carbon dioxide.

The catalytic, vapor phase oxidation of furfural has attracted considerable attention, primarily as a means for the production of maleic acid or anhydride. Generally speaking, the procedure involves passage of the aldehyde and an oxygen-containing gas at elevated temperature over a vanadium pentoxide catalyst which may be modified by incorporation of other metallic oxides, principally molybdenum. The early work of Sessions[498] (see also [499]) was followed by patents to Zumstein,[500] Boehringer,[501] Witzel,[502] The Selden Company,[503] Jaeger,[504] Milas and Walsh[505]; and more recently, Nielsen[506] (see also [507]) has reviewed the subject, and has pointed out several important factors which influence successful operation.

Electrolytic oxidation in dilute sulfuric acid medium likewise gives rise to maleic acid, by way of the intermediate aldehydic acid, β-formylacrylic

[494] Moureu, Dufraisse and Lotte, *Compt. rend.*, **180**, 993 (1925).

[495] Comstock and Reeves (to Bay Chemical Co.), U. S. Pat. 2,426,143 (1947); *C. A.*, **41**, 7415 (1947).

[496] Comstock and Reeves (to Bay Chemical Co.), U. S. Pat. 2,382,207 (1945); *C. A.*, **40**, 365 (1946).

[497] Comstock (to Bay Chemical Co.), U. S. Pat. 2,384,238 (1945); *C. A.*, **40**, 365 (1946).

[498] Sessions, *J. Am. Chem. Soc.*, **50**, 1696 (1928).

[499] Milas and Walsh, *J. Am. Chem. Soc.*, **57**, 1389 (1935).

[500] Zumstein (to C. H. Boehringer Sohn A.-G.), U. S. Pat. 1,956,482 (1934); C. A., **28**, 4071 (1934); German Pat. 478,726 (1927); *C. A.*, **23**, 4712 (1929); German Pat. 539,269 (1927); *C. A.*, **26**, 2989 (1932).

[501] Boehringer, A. (trading as C. H. Boehringer Sohn), British Pat. 285,426 (1927); *C. A.*, **22**, 4539 (1928); British Pat. 297,667 (1927); *C. A.*, **23**, 2724 (1929).

[502] Witzel (to Selden Co.), U. S. Pat. 1,945,246 (1934); *C. A.*, **28**, 2370 (1934).

[503] The Selden Co., British Pat. 355,192 (1930); *C. A.*, **26**, 4061 (1932).

[504] Jaeger (to American Cyanamid and Chemical Corp.), U. S. Pat. 1,995,614 (1935); *C. A.*, **29**, 2975 (1935).

[505] Milas and Walsh (to Research Corp.), U. S. Pat. 2,118,567 (1938); *C. A.*, **32**, 5409 (1938).

[506] Nielsen, *Ind. Eng. Chem.*, **41**, 365 (1949).

[507] Nielsen (to The Quaker Oats Co.), U. S. Pat. 2,421,428 (1947); C. A., **41**, 5551 (1947); U. S. Pat. 2,464,825 (1949); *C. A.*, **43**, 4700 (1949).

acid.[508, 509] With a higher concentration of sulfuric acid, Yabuta[510, 511, 512] obtained a mixture of maleic and succinic acids as the major products.

Most of the common oxidizing agents have been applied to furfural at one time or another, and while in many instances nuclear and side chain oxidation may to some extent proceed simultaneously, the available information indicates that acidic conditions favor attack on the nucleus, and alkaline conditions promote oxidation of the formyl group. Thus, in basic medium using silver oxide, permanganate, etc., furoic acid may be obtained in high yield (p. 488). However, if the reagent is vigorous, and is available in sufficient quantity, oxidation can proceed further in alkaline medium with formation of maleic acid or related compounds and/or their oxidation products. For example, Obata[513] reports the oxidation of furfural to maleic acid with alkaline permanganate at 0–3°. It is apparent that this reaction proceeds stepwise with furoic salt as an intermediate; that is, in alkaline medium, attack on the nucleus occurs subsequent to oxidation of the formyl group to carboxyl; if not completely, at least predominantly in this order. (For a postulated mechanism of the oxidation of furoic acid to maleic acid, see p. 495).

$$C_4H_3O\text{—}CHO \xrightarrow[KOH]{KMnO_4} C_4H_3O\text{—}COOK \xrightarrow[KOH]{KMnO_4} KOOC\text{—}CH{=}CH\text{—}COOK$$

The mechanism of reaction using acidic oxidizing agents, or where the medium is allowed to become acidic, appears to be different in at least one important aspect. That is, while the oxidation product(s) is generally β-formylacrylic (I), maleic (II), or fumaric acid (II), or compounds formed by further action of the reagent on these acids, it is doubtful that furoic acid is a major intermediate. Thus, at this writing, there has been no confirmed report of a high yield of furoic acid by oxidation of furfural under acidic conditions. It is believed that this is due to facile nuclear oxidation; and that in acidic medium, this mode of attack takes precedence over oxidation of the formyl group. This was clearly demonstrated in two instances which were discussed earlier (pp. 385), (1) autoxidation, and (2) the action of peracetic acid, both giving rise to formylacrylic acid (I), with formic acid, in practically quantitative yield, as the other degradation product. Little or no furoic acid is found, and as pointed out previously, if this product

[508] Hellström, *Svensk Kem. Tid.*, **60**, 214 (1948); *C. A.*, **43**, 1271 (1949).

[509] Deribas, Shvartzberg and Il'inskii, Russian Pat. 40,972 (1935); *C. A.*, **30**, 7127 (1936).

[510] Yabuta and Shimose, from magazine issued by The Nikon Nogei Kagaku Kai, Japan, April, 1928.

[511] Yabuta, British Pat. 253,877 (1925); *C. A.*, **21**, 2439 (1927).

[512] Yabuta (to Zaidan Hojin Rikagaku Kenkyujo), U. S. Pat. 1,709,297 (1929) *C. A.*, **23**, 2667 (1929).

[513] Obata, *J. Agr. Chem. Soc. Japan*, **16**, 187 (1940); *C. A.*, **34**, 5840 (1940).

were the precursor of I, carbon dioxide, not formic acid[j], would have been split out. Milas[514] (see also [515]) does report carbon dioxide and fumaric acid (II) as the products when furfural is oxidized in aqueous solution[k] with chlorate ion (2.1–2.5 moles per mole of furfural) in the presence of vanadium pentoxide, and he concluded that they were formed by way of furoic acid. In our view this is doubtful; it is more likely that they have their origin in the postulated intermediate B. In further support of the thesis that furoic acid is not a major intermediate when furfural is oxidized under acidic conditions, it has been observed that treatment of the aldehyde in aqueous solution with an equimolecular quantity of bromine fails to produce carbon dioxide, and equally important, none of the readily isolable furoic acid is found.[1, 105] Similar treatment of furoic acid results in copious evolution of carbon dioxide.

The following diagram purports to explain the formation of most of the products which have been isolated when furfural is oxidized under acidic conditions; with aqueous bromine,[516] alcoholic bromine,[483, 517, 518] chlorate ion,[514, 519, 520, 521, 522, 523, 524] chlorine dioxide,[525, 526] hydrogen peroxide,[527] peracetic acid,[485] nitric acid,[510] and with Caro's reagent.[528] In most instances, maleic acid or related compounds are the major products, and these can be accounted for most satisfactorily in terms of the intermediate 1,4-

[j] Note that in some instances carbon dioxide may arise by oxidation of previously formed formic acid.

[k] Initially the medium was approximately neutral, or in some cases, was made acidic by addition of sulfuric acid. However, even in the former instance, the medium becomes acidic due to the formation of acidic products.

[1] The product is unstable, and has not yet been adequately characterized. We believe it to be intermediate B, whereas Hughes and Acree[516] postulate a ketodihydrofurfural structure, on the basis of the composition of a derivative with phenylhydrazine. See further discussion in the text which follows.

[514] Milas, *J. Am. Chem. Soc.*, **49,** 2005 (1927).

[515] Buluigina, Masloboino-Zhirovoe Delo, **1934,** No. 4, 43; *C. A.*, **30,** 1743 (1936).

[516] Hughes and Acree, *J. Research Natl. Bur. Standards*, **24,** 175 (1940).

[517] Fakstorp, Raleigh and Schniepp, *J. Am. Chem. Soc.*, **72,** 869 (1950).

[518] Meinel, *Ann.*, **516,** 231 (1935).

[519] Milas, "Organic Syntheses," Collective Vol. II, p. 302, New York, John Wiley and Sons (1943).

[520] Sah, *Z. Vitamin-, Hormone- u. Fermentforsch.*, **3,** 40 (1949); *C. A.*, **44,** 5857 (1950).

[521] Takahasi (to Sankyo K. K.), Japanese Pat. 137,755 (1940); *C. A.*, **35,** 1806 (1941).

[522] Takehara, *J. Soc. Chem. Ind. Japan*, **47,** 496 (1944); *C. A.*, **42,** 6753 (1948).

[523] Serdyukov, *Masloboino-Zhirovoe Delo*, **1934,** No. 4, 43; *C. A.*, **30,** 1769 (1936).

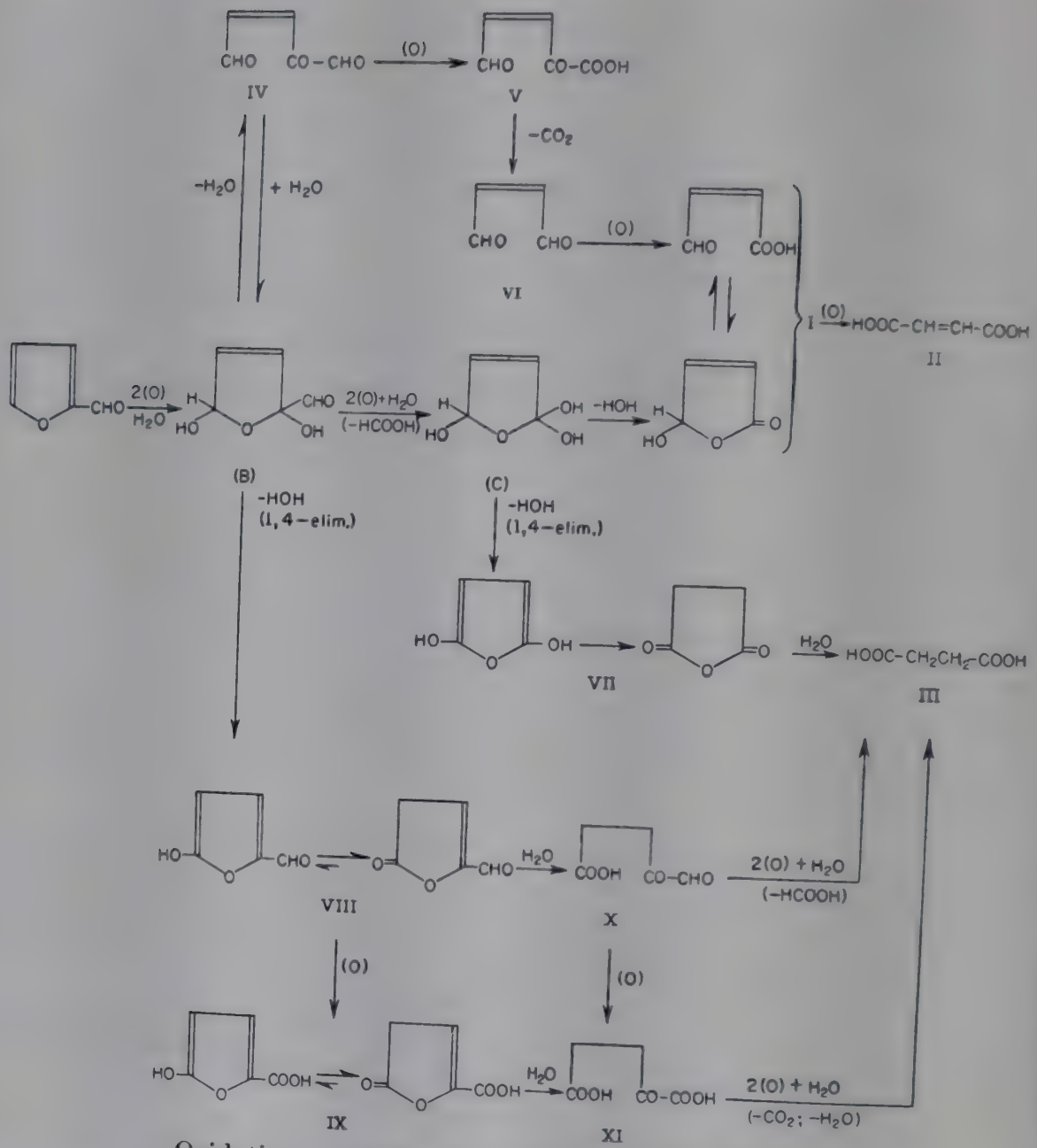
[524] Serdyukov and Andrew, Russian Pat. 38,145 (1933); *Chem. Centr.*, **1935, II,** 2581.

[525] Schmidt and Atterer, *Ber.*, **60,** 1671 (1927).

[526] Schmidt, Haag, Abele and Sperling, *Ber.*, **58,** 1394 (1925).

[527] Cross, Bevan and Heiberg, *J. Chem. Soc.*, **75,** 747 (1899); *Proc. Chem. Soc.*, **15,** 130 (1899).

[528] Cross, Bevan and Briggs, *Ber.*, **33,** 3132 (1900).



Oxidation of Furfural in Aqueous, Acidic Medium

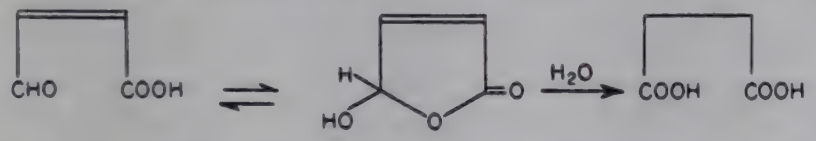
hydroxylation[m] adduct, 2,5-dihydroxy-2,5-dihydrofurfural, B. By further oxidation B can give rise to β-formylacrylic acid, I, and formic acid; thence to maleic or fumaric acids, II, the latter[519] presumably by isomerization of maleic acid in hot, aqueous, acidic medium. *Meso*-tartaric and oxalic acids reported by Milas[514] presumably arise by the action of chlorate ion on II, or possibly by way of 1,2-hydroxylation of the C=C bond of B or C. Milas[514] also isolated, in approximately 20 per cent yield, the barium salt of a dicarboxylic acid to which he assigned the formula $C_5H_4O_5$. However,

[m] It is recognized that the radicals actually added may vary depending upon the nature of the reagent. That is, aqueous bromine may add as HOBr; alcoholic bromine as ROBr, etc. In aqueous, acidic medium such groups would be replaced readily by OH, and for convenience the oxidation is illustrated in terms of hydroxylation. Note, later in text, that with alcoholic bromine, Clauson-Kaas was able to isolate dialkoxydihydrofurans.

the analytical data (C, H, Ba) fit equally well the formula $C_5H_6O_5$ for the acid, and we are inclined to believe that it is α-ketoglutaric acid, XI.[n] What may be the same dicarboxylic acid, XI, was also isolated (as Ba salt) as a product of the action of Caro's acid on furfural. In this instance the major products were succinic and formic acids, and in lesser quantity, what was reported to be 5-hydroxyfurfural, VIII.[528] However, as Clauson-Kaas[483] has pointed out, the latter was undoubtedly β-formylacrylic acid, I; certainly the nitrogen analyses reported for the phenyl- and methylphenylhydrazone derivatives are in better agreement with I than with VIII, and the reported melting points check closely with those observed for the corresponding derivatives of I. Furthermore, Cross, Bevan and Briggs[528] showed that the phenylhydrazone was soluble in cold, dilute ammonia, and could be reprecipitated unchanged by addition of acid, a property consistent with its formulation as a hydrazone of I. Clauson-Kaas[529, 483] has offered an explanation of the formation of succinic acid types which involves 1,4-elimination of water from the intermediate 2,5-dihydroxy-2,5-dihydrofurans.[o] Thus, he proposes that intermediate C can be transformed into succinic anhydride, VII, and by analogy, B could give rise to 5-hydroxyfurfural which we would expect to exist in the form of the isomeric lactone, VIII. What may have been VIII[p] was actually isolated, in the form of a

[n] Clauson-Kaas and Fakstorp[483] propose that the product is a ketoglutaconic acid, HOOC—CH=CH—CO—COOH, having its origin in V. However, in our view V, if formed at all, would have a very transitory existence since it is a vinylog of a β-carbonyl carboxylic acid, and under the conditions employed by Milas would immediately undergo decarboxylation (see also p. 495).

[o] Another possible mode of formation has also been pointed out by Clauson-Kaas.[529] Thus, he calls attention to the hydrolytic rearrangement of formylacrylic acid, I, to succinic acid under the influence of aqueous potassium cyanide.[530, 485] While there

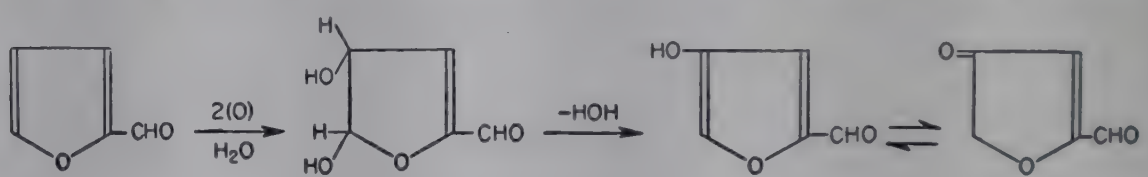


is no evidence for such transformation under other conditions, the possibility of obtaining saturated types from I and related β-carbonyl acrylic acids should not be overlooked. However, if the formation of succinic types (i.e., III, XI, etc.) actually does occur by the alternate route of 1,4-elimination of water from 2,5-dihydroxy-2,5-dihydrofuran intermediates, one might expect to find them in greater yield where conditions favor dehydration. In this connection, note that succinic acid, III, is the major product when furfural is oxidized with Caro's acid.[528] Furthermore, Milas'[514] conditions of elevated temperature might be expected to favor such elimination, and he did obtain, in sizable yield, a product which we have earlier (see text) postulated to be XI.

[p] Clauson-Kaas and Fakstorp[483] are of the opinion that this too was a derivative of β-formylacrylic acid, I. We would agree with them that I was actually formed as a major product, but in our opinion, I escaped detection by Cross, Bevan and Heiberg[527] because of the mode of isolation of the products of reaction. That is, direct precipitation of derivatives by addition of phenylhydrazine to the reaction mixture produced a large quantity of reddish-orange material which could not be separated

phenylhydrazone, by the action of aqueous hydrogen peroxide on furfural.[527] Also obtained, in approximately 5 per cent yield as the barium salt, was a monocarboxylic acid[q] which may have been either the corresponding lactone carboxylic acid, IX, formed by oxidation of VIII, or the ketoglutaraldehydic acid, X, derived from VIII by hydrolysis.

The product of reaction of furfural with one mole of bromine in cold, aqueous, acidic medium has not been isolated, but the experimental evidence[516] shows that it contains no bromine, and indicates it to be a C_5 compound. Thus, Hughes and Acree[516] precipitated a derivative directly from the reaction mixture by addition of phenylhydrazine, and on the basis of its composition, $C_{17}H_{16}N_4O$, proposed that it was the dihydrazone of a keto-dihydrofurfural, XIII, derived by loss of the elements of water from XII as shown below. However, we know that the major product of



XII XIII

further oxidation with this, and other acidic reagents, is maleic acid or a

satisfactorily into its component parts. Accordingly, Cross, Bevan and Heiberg introduced a preliminary step which involved separation of the acidic products as barium salts, and we would expect this treatment to have precipitated any I which was present. The filtrate was then treated with phenylhydrazine, and a hydrazone was obtained (no m.p. given); calculated for $C_5H_4O_2{=}NNHC_6H_5$: C, 65.35%; H, 4.95%; N, 13.80%; found, C, 65.33%; H, 4.92%; N, 13.10%. The calculated composition of the phenylhydrazone of I is C, 63.16%; H, 5.32%; N, 14.74%. The analysis found is obviously closer to that of a hydroxyfurfural derivative (i.e., VIII) than to a hydrazone of I.

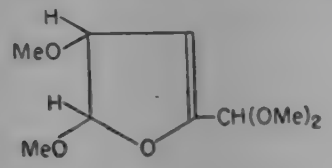
Argument has already been given (see text) that the product obtained by Cross, Bevan and Briggs[528] was I and not 5-hydroxyfurfural as they supposed. However, these workers were able to show that their product was different from that of Cross, Bevan and Heiberg (further evidence that the latter was not I). Cross, Bevan and Briggs proposed that Cross, Bevan and Heiberg's product was 3-hydroxyfurfural which, in our opinion, is a highly improbable structure. In the absence of further evidence, we favor structure VIII for the product isolated as a phenylhydrazone by Cross, Bevan and Heiberg.

[q] Clauson-Kaas and Fakstorp[483] suggested that this acid was V, derived from 2,5-dihydroxy-2,5-dihydrofuroic acid (p. 495). We seriously doubt that either of these products can exist; they would be expected to undergo decarboxylation immediately. Cross, Bevan and Briggs[528] believed the acid to be 3-hydroxyfuroic acid, which is very unlikely. Analysis of barium salt:

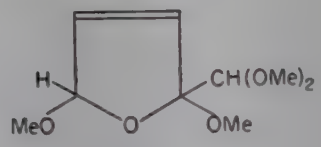
Found[527]	Calc'd for IX $Ba(C_5H_3O_4)_2$	Calc'd. for X $Ba(C_5H_5O_4)_2$
% Ba 35.55	35.04	34.75
% C 30.83	30.69	30.35
% H 2.19	1.53	2.53

[529] Clauson-Kaas, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd*, **24**, No. 6, 18 pp. (1947); *C. A.*, **42**, 1930 (1948).

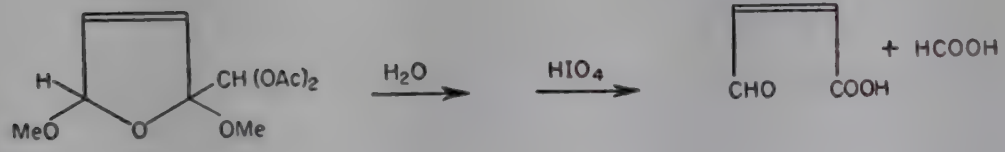
related compound. Accordingly, the derivative isolated by Hughes and Acree is more reasonably a product of 1,4-hydroxylation of furfural, and as has been suggested elsewhere,[483] we believe it to be a dihydrazone[r] of IV. Related to this is the work of Meinel[518] on the action of methanolic bromine on furfural. He postulated 1,2-methoxylation, and the structure XIV for his product. However, similar treatment of furfurylidene diacetate was later[483] shown to produce a product, XVI, which could be cleaved with periodic acid to β-formylacrylic acid. Accordingly, Meinel's product is more reasonably formulated as 2,5-dimethoxy-2,5-dihydrofurfural methyl acetal, XV.[483, 529] (For the corresponding diethoxydihydrofurfural ethyl acetal, see Fakstorp, Raleigh and Schniepp[517]; for 2,5-diacetoxy-2,5-dihydrofurfural diacetate from furfural by the action of bromine in acetic acid containing potassium acetate, see Clauson-Kaas[530a]). The relationship of XV and XVI to intermediate B will be readily apparent.



XIV



XV



XVI

From furfural and five moles of bromine in hot, aqueous solution, Simonis[531] obtained in good yield, α,β-dibromo-β-formylacrylic acid, XVII, the so-called mucobromic acid. The chlorine analog has been similarly obtained by the action of aqueous chlorine on the aldehyde[105] (see also [531a, 531b, 532]). These reactions are also subject to interpretation in terms of a 1,4-addition intermediate, although in this instance, because of the availability of more reagent, it is here suggested that further addition takes

[r] While IV might be expected to form a trisphenylhydrazone, it is not unreasonable to suppose that the more reactive formyl groups condense more rapidly than the ketone group, and that before the latter can react, the dihydrazone is precipitated from the aqueous medium.

[530] Fecht, *Ber.*, **38**, 1272 (1905).

[530a] Clauson-Kaas (to Kemisk Vaerk Koge A/S), U. S. Pat. 2,514,026 (1950); *C. A.*, **44**, 8375 (1950).

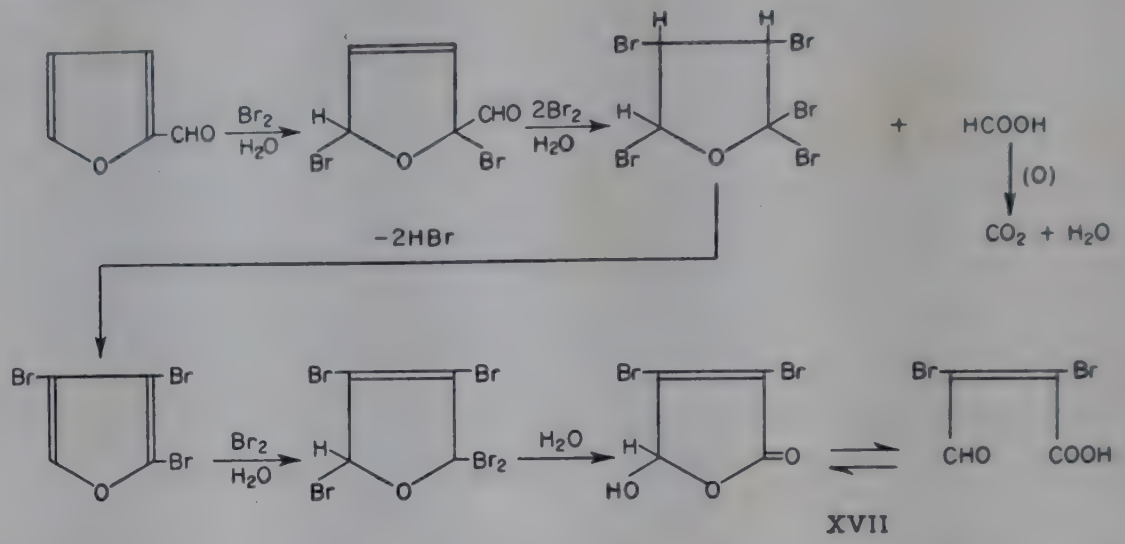
[531] Simonis, *Ber.*, **32**, 2084 (1899).

[531a] Beattie, Heilbron and Irving, *J. Chem. Soc.*, **1932**, 260.

[531b] Gryszkiewicz-Trochimowski, Schmidt and Gryszkiewicz-Trochimowski, *Bull. soc. chim. France*, **1948**, 593.

[532] Leder, Russian Pat. 48,297 (1936); *Chem. Centr.*, **1937**, II, 288.

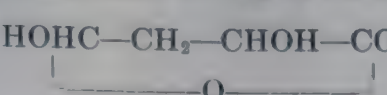
place at the 3,4-double bond. The resulting product is presumed to undergo dehydrohalogenation, then 1,4-addition, and finally, hydrolysis to XVII (see also pp. 497, 119).



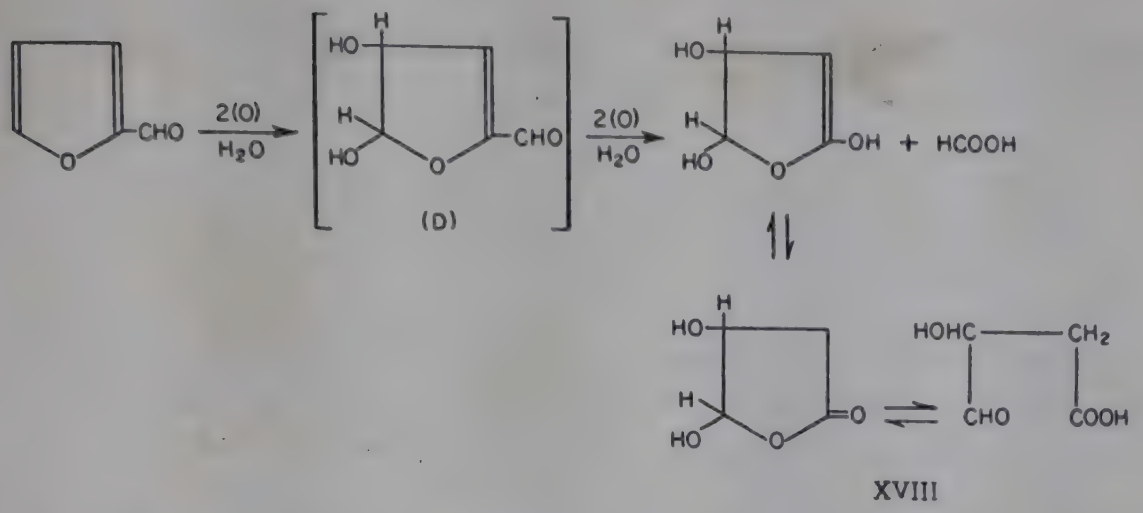
Up to this point it has been possible to explain all of the products of oxidation by way of a common intermediate type, 2,5-dihydroxy-2,5-dihydrofurfural, or related products. However, it would be somewhat surprising if 1,4-addition to the furan nucleus took place to the complete exclusion of 1,2-type adducts. In the work of Boeseken[485] we find reference to a product which is most satisfactorily explained by postulating an intermediate of the latter type. When furfural was treated with two moles of 70 per cent peracetic acid, Boeseken found formic acid, maleic acid, and an aldehydo carboxylic acid, $C_4H_6O_4$, which apparently exists in the hemiacylal form. He proposed that this product was related to malic acid as formylacrylic acid is to maleic acid, and we propose that it is XVIII,[s] formed by way of 4,5-dihydroxy-4,5-dihydrofurfural, D, as indicated below.

It will be apparent that the oxidation of furfural presents a complex problem from several standpoints. Certainly, there are many factors which influence the course of reaction, including such obvious variables as the type, quantity and rate of addition of the oxidizing agent, the temperature, and the nature of the solvent medium. Much work remains to be done, and a complete and unequivocal understanding of the many reactions involved

[s] Boeseken[485] proposed that it was either XVIII or its isomer,



It is possible to account for the latter by way of 2,3-dihydroxy-2,3-dihydrofurfural. However, this isomer is equivalent to a β-hydroxy aldehyde, and in accordance with the behavior of such types, would be expected to lose the elements of water even on relatively mild heating. Boeseken obtained his product (b.p. 49–50° (cathodic vac.)) by distillation; hence, we favor structure XVIII.



XVIII

must await the outcome of future investigations. It is hoped that this resumé of the subject will serve to stimulate research on this interesting facet of furan chemistry.

Resinification

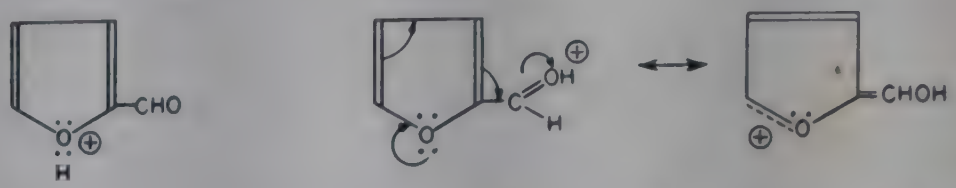
On long standing, furfural slowly resinifies to a black gel consisting mainly of unchanged furfural. Thus, Berthelot and Rivals[533] described a sample of the aldehyde which had been stored in a closed container for several years and which had solidified. On vacuum distillation, however, approximately 90 per cent by weight distilled over, leaving a brilliant, black, friable resin, the analysis of which corresponded to three molecules of furfural less one of water.

The resinification is accelerated by heating but even at 230°, many hours exposure are required to produce detectable changes in the physical properties of furfural. Dunlop and Peters[15] measured the extent of destruction at elevated temperatures in sealed glass tubes: 0.28 per cent decomposition after 280 hours at 140°; at 180° for 185 hours, only 0.32 per cent decomposition. These observations are in keeping with the very low loss of furfural experienced in oil refining operations in which the aldehyde may be exposed to temperatures in the range 230–275° for short periods during each cycle.

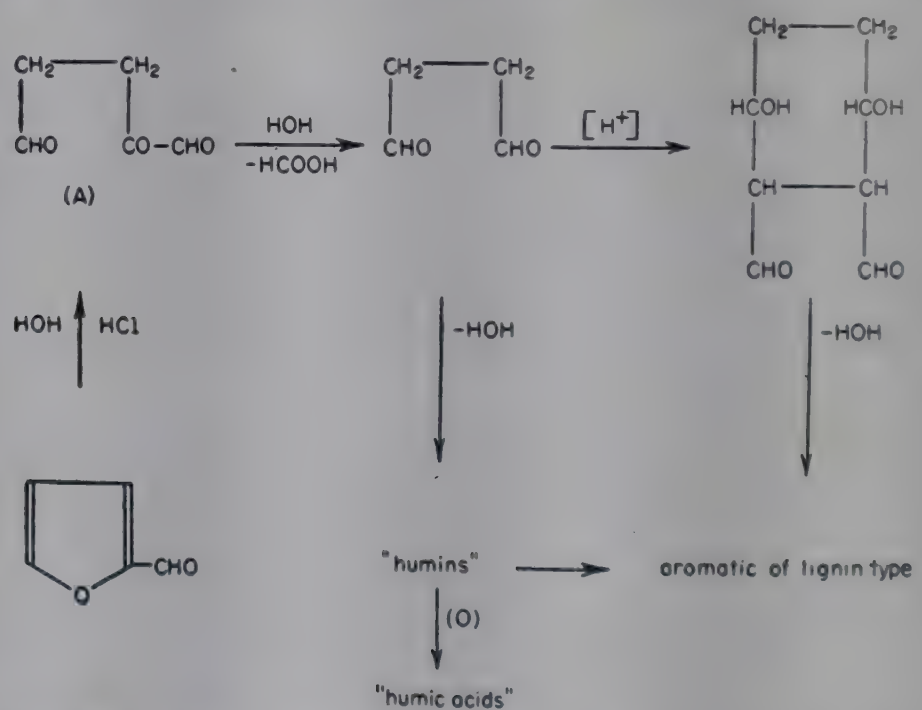
On the other hand, acidic materials markedly accelerate the rate of resinification, and numerous patents have issued relating to resin formation in this manner. The resins so formed are brittle in nature and possess little strength so that few industrial applications have resulted. Suitable catalysts include not only the mineral and strong organic acids, but also acidic salts and the halides of the elements of groups 3, 4, and 5 of the periodic table.[534] The catalytic action of acids may be attributed to the loss of resonance

[533] Berthelot and Rivals, *Compt. rend.*, **120**, 1086 (1895).
[534] Calloway, *Iowa State Coll. J. Sci.*, **9**, 141 (1934).

stability of the furfural molecule by bonding at the nuclear oxygen atom, or at the aldehyde group, or both.



Several attempts have been made to elucidate the structure of the furfural resin and the mechanism of its formation. Marcusson[535, 536, 537] became interested in the acid-catalyzed resinification reaction in connection with the origin of natural humins and humic acids from cellulose. He prepared synthetic humins by the action of acids on various furan compounds, and proposed the following scheme to account for the resinification of furfural. According to this hypothesis, succinaldehyde is an intermediate product

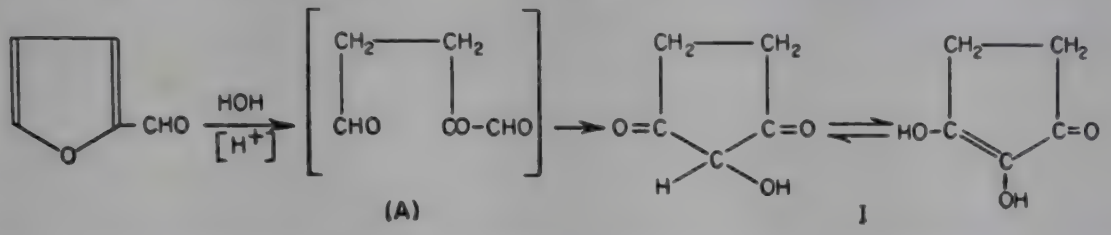


which resinifies to humin-like material by aldolization and dehydration. Earlier, Gortner[538] had called attention to a possible relationship between furfural and humins when he obtained a humin-like, water-insoluble material by heating the aldehyde with hydrochloric acid. Under similar conditions, Schütz, Sarten and Meyer[539] (see also [540]) report "artificial lignin"

[535] Marcusson, *Z. angew. Chem.*, **32**, 113 (1919); *Chem. Centr.*, **1919**, **IV**, 124.
[536] Marcusson, *Chem. Ztg.*, **44**, 43 (1920); *C. A.*, **14**, 2321 (1920).
[537] Marcusson, *Ber.*, **58**, 869 (1925).
[538] Gortner, *J. Biol. Chem.*, **26**, 195 (1916).
[539] Schütz, Sarten and Meyer, *Holzforschung*, **1**, 2, (1947); *C. A.*, **42**, 1419 (1948).
[540] Müller and Stalder, *Papier-Fabr.*, **36**, Tech. Tl., 81 (1938); *C. A.*, **32**, 4329 (1938)

from furfural, and Blanksma and Egmond[541] have recently described humin formation from 5-(hydroxymethyl)furfural and hydrochloric or oxalic acids.

Another indication of ring cleavage when furfural is heated with aqueous acids is to be found in the patent literature[542] where reductic acid, I, is reported in *ca.* 1 per cent yield by autoclaving furfural with 8 per cent sulfuric acid at 160° for 1.5 hours. The reaction can be formulated as a cleavage of the furan ring followed by recyclization by an intramolecular



acyloin condensation. The proposed intermediate, α-ketoglutaraldehyde (A) is common to this and to Marcusson's mechanism (above), and on this basis, ring closure of A to I is competitive with hydrolytic fission of A to succinaldehyde and formic acid.

A study of the kinetics of destruction of furfural in dilute, acidic, aqueous medium has been made by Williams and Dunlop[543] (see also [544, 545]) who found the reaction to be pseudo-unimolecular; the rate is directly proportional to the concentration of hydrogen ion, and to the concentration of furfural in the range of 1–2 per cent. While formic acid was identified as one product of the reaction, no evidence for autocatalysis was observed in this study, attributable to the almost negligible effect of the formic acid on the active acidity of the systems employed. The temperature effect was determined and employed to derive the Arrhenius equation from which the energy of activation was calculated to be approximately 20 kcal. per mole. The titratable acidity increased during the destruction of furfural, but at no time, in this work, did it exceed two-thirds of an equivalent per mole of furfural destroyed. Part of this increase is due to formic acid, but a portion is also due to the acidic nature of some of the resinous products which are formed simultaneously. Accordingly, Marcusson's proposed mechanism can be only partially true. Nor can the formation of reductic acid account for the balance of destruction inasmuch as this mechanism also requires one equivalent of acidity per mole of furfural

[541] Blanksma and Egmond, *Rec. trav. chim.*, **65**, 309 (1946).

[542] Wessanen's Koninklijke Fabrieken N. V., Dutch Pat. 61,296 (1948); *C. A.*, **42**, 7788 (1948).

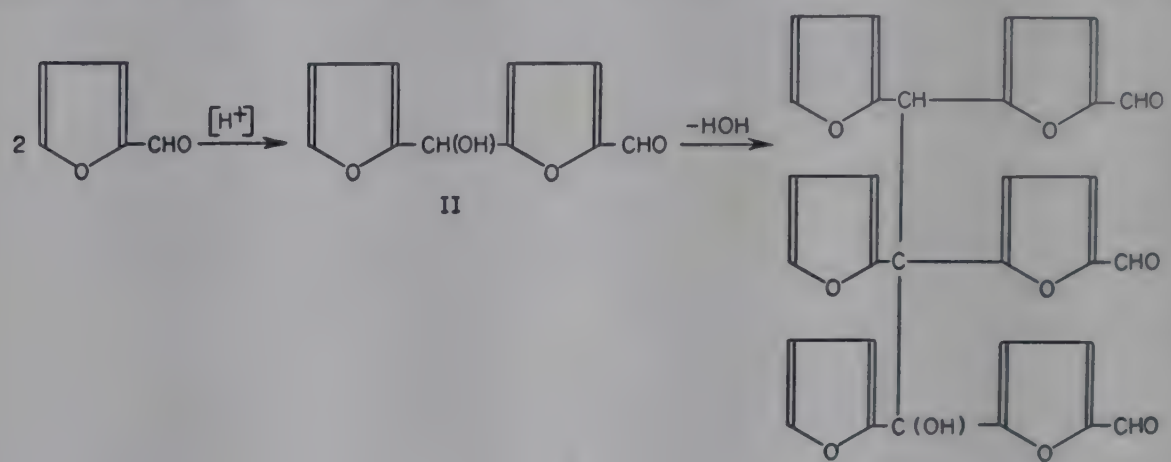
[543] Williams and Dunlop, *Ind. Eng. Chem.*, **40**, 239 (1948).

[544] Lazarev, *Org. Chem. Ind., U.S.S.R.*, **6**, 258 (1939); *C. A.*, **34**, 2371 (1940).

[545] Curtis and Hatt, *Australian J. Sci. Research*, Ser. A, **1**, 213 (1948).

destroyed. The recent proposal of Takano and Tsuruta[546] may offer a solution to the problem. These workers suggest that part of the furfural is cleaved to succinaldehyde which then condenses with unchanged furfural.

At variance with these possible mechanisms is yet another which does not involve cleavage of the furan nucleus. Thus, Illari[547] suggests that the resinification proceeds by an aldol-type condensation involving the hydrogen atoms attached to the number 5 carbon atom of the nucleus, and subsequent intermolecular dehydration of the carbinol (II) so formed as illustrated below. He considers the propanol derivative, III, as a base structure which subsequently polymerizes to form the "furfural blacks" obtained by heating



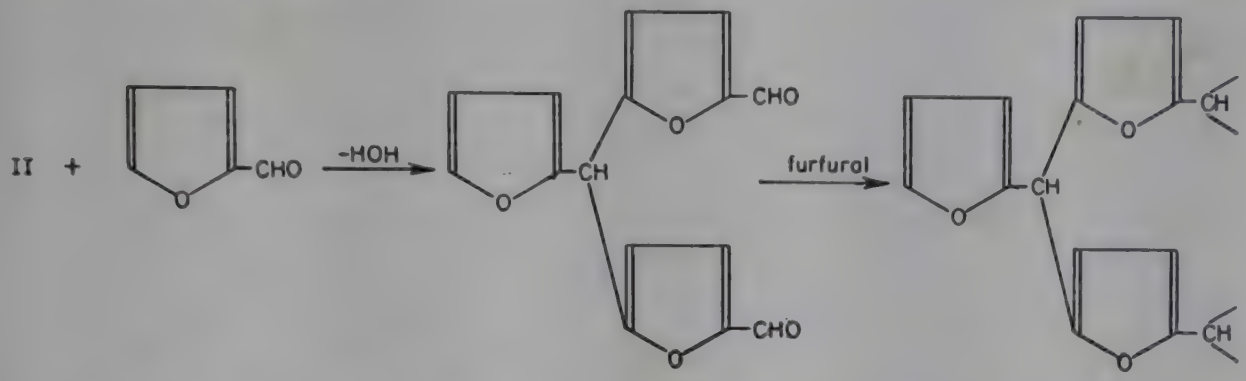
furfural with hydrochloric acid (d. 1.19, or d. 1.06) or with 50 per cent hydriodic acid. The final, infusible, insoluble resins analyzed for $(C_3H_2O)_n$,[t] reduced hot Fehling's solution, and gave rise to succinic anhydride following oxidation with neutral (but not acid or alkaline) potassium permanganate. Reaction of the resin with excess aqueous bromine produced a water-insoluble yellow substance which was soluble in alcohol and in acetic acid, but which gave no identifiable products. This mechanism fails to account for the formation of formic acid observed by Marcusson, nor does it explain the acidic resins found by Williams and Dunlop. Furthermore, the latter investigators report pseudo-unimolecular kinetics, whereas Illari's mechanism would indicate a reaction of second order with respect to the concentration of furfural. In this regard it must be noted, however, that the concentration of furfural in Illari's experiment was approximately 10–15 times that employed by Williams and Dunlop, and little kinetic data have been reported for concentrations in this range (see [545]).

[t] Furoin, under similar conditions, produced a resin of the same empirical constitution.[547]

[546] Takano and Tsuruta, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **70**, 335 (1949); *C. A.*, **45**, 3190 (1951).

[547] Illari, *Gazz. chim. ital.*, **77**, 389 (1947); *C. A.*, **42**, 2959 (1948).

Actually, the resinification of furfural may be a complex reaction involving all of the mechanisms which have been discussed, and perhaps also that outlined below which goes forward by way of Illari's proposed intermediate, the carbinol, II.



Since the resinification reaction is catalyzed by acids, it is not surprising to find many reports of the use of basic substances as inhibitors (see [548, 549, 550]). Strong alkalies must be avoided, however, since these induce a different type of destruction (Chapter 14), but incremental addition of weaker bases, or of buffer compounds, does significantly decrease the rate of resinification of furfural when subjected to elevated temperatures.

Deterioration of furfural and resinification in the presence of air or oxygen is considered elsewhere (p. 385).

Reaction of Furfural with Phenols

The characteristic condensation reactions of aldehydes with the active *o*- and *p*-hydrogen atoms of phenols are also displayed by furfural. However, although the early work on reactions of this type dates back to the studies of Baeyer[460] in 1877, comparatively little has been reported with regard to the structure and mechanism of formation of the complex resinous products obtainable by this means. To date, the major interest has been focused on potential industrial applications of furfural-phenolic resins, and the patent literature on this subject is now voluminous (see [551, 552, 553, 554, 555]).

The formation of resins by reaction of furfural with substituted phenols,

[548] Schulze and Hillyer (to Phillips Petroleum Co.), U. S. Pat. 2,485,070 (1949); *C. A.*, **44**, 2564 (1950).

[549] Mertz (to Phillips Petroleum Co.), U. S. Pat. 2,409,781 (1946); *C. A.*, **41**, 278 (1947).

[550] Schulze and Hillyer (to Phillips Petroleum Co.), U. S. Pat. 2,440,451 (1948); *C. A.*, **42**, 6166 (1948).

[551] Trickey, Miner and Brownlee, *Ind. Eng. Chem.*, **15**, 65 (1923).

[552] Peters, *Ind. Eng. Chem.*, **28**, 755 (1936).

[553] Peters, *Modern Plastics*, **13**, 38 (1936).

[554] Norton, *Ind. Eng. Chem.*, **40**, 236 (1948).

[555] Dunlop and Peters, in Alexander, "Colloid Chemistry," Vol. VI, p. 1048, New York, Reinhold Publishing Corp. (1946).

naphthols, and related types was studied by Beckman and Dehn.[556] Tzonev and Yavnel[557] report the reaction velocity with several phenolic compounds to increase in the following order: *p*-hydroquinone, *o*-hydroquinone, β-naphthol, phenol, cresols, α-naphthol, resorcinol. More recently, Hachihama and his co-workers[558] embarked on an extensive study designed to throw light on the composition and mode of formation of furfural-phenol resins. The soluble resin obtained using ammonia as the condensing agent, or when phenol is employed in excess, gives rise to furoic acid on oxidation with hydrogen peroxide. On the other hand, insoluble resins formed in the presence of hydrochloric acid, or by using an excess of furfural, are oxidized to 2,5-furandicarboxylic acid, indicating involvement of the number 5 carbon atom of the furan nucleus in this resinification reaction. That both *o*- and *p*-condensation take place is supported by the isolation of salicylic acid as an oxidation product, and of anisic acid when the resin is methylated prior to oxidation. Also included in Hachihama's work was the measurement of water-formation during resinification, and the use of this information to calculate molecular weight in accordance with this proposed scheme of reaction. Catalytic (Ni-R) hydrogenation of the resin was observed to halve the molecular weight, and to reduce the color, the latter suggesting that the source of color resides in the furan nuclei contained in the resin molecule. From data obtained on *p*-nitrobenzoylation of the resin obtained by condensing an equimolecular mixture of furfural and phenol in benzene under the influence of hydrogen chloride, Hachihama concluded that a new phenolic hydroxyl group is formed during the course of reaction. Among other factors which he studied was the effect of various salts and bases on the rate of resinification.

The initial reaction of phenol with furfural appears to proceed analogously to that of phenol with formaldehyde. Thus, Porai-Koschitz *et al.*[559, 560] report the isolation of a product which analyzed correctly for (*o*- or *p*-hydroxyphenyl)furylcarbinol. A consistent melting point could not be obtained, but two derivatives were prepared, (*o*- or *p*-benzyloxyphenyl)furylcarbinol (m.p. 161–162°) and the corresponding acetic ester (m.p. 285–287°). With the trihydric phenol, phloroglucinol, reaction

[556] Beckman and Dehn, *Sitzb. kgl. preuss. Akad. Wiss.*, **1918**, 1201; *C. A.*, **14**, 642 (1920).

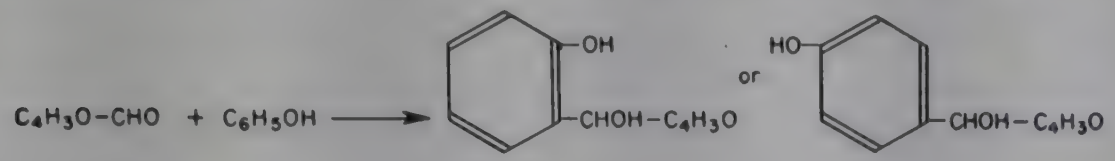
[557] Tzonev and Yavnel, *Masloboino-Zhirovoe Delo*, **1932**, 38; *C. A.*, **27**, 3471 (1933).

[558] Hachihama *et al.*, *J. Soc. Chem. Ind. Japan*, **45**, 1053 (1942); **46**, 520, 808 (1943); **47**, 178, 180, 183, 186, 220, 359, 657, 659, 824 (1944); **49**, 61 (1946); *C. A.*, **43**, 5224–5226 (1949).

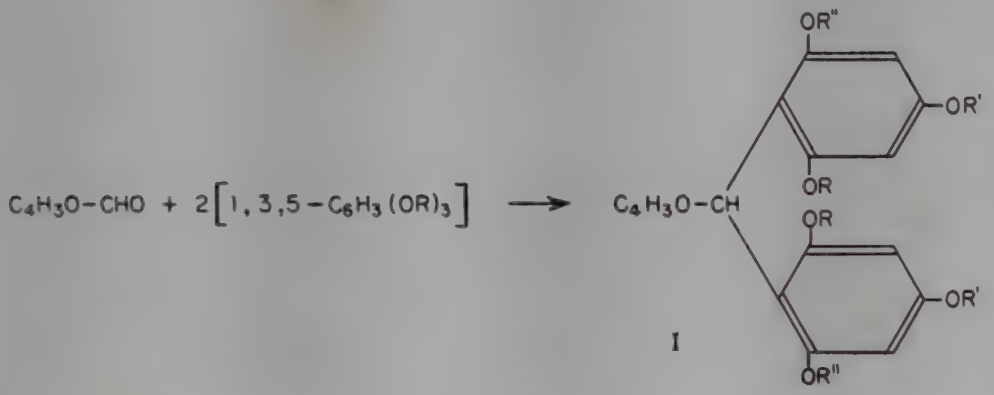
[559] Porai-Koshitz, Kudryavtzev and Mashkileizon, *Kunstoffe*, **23**, 97 (1933); *C. A.* **27**, 3709 (1933).

[560] Porai-Koshitz, Kudryavtzev and Mashkileizon, *J. Applied Chem. U.S.S.R.*, **6**, 685 (1933); *C. A.*, **28**, 4055 (1934).

with furfural in acidic medium proceeds in a similar manner, although the simplest isolated product corresponds to the condensation of the aldehyde



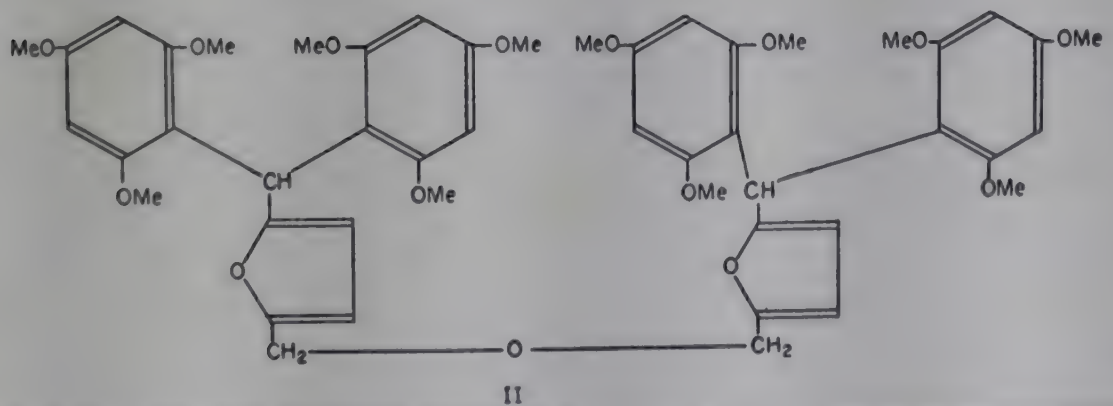
with two moles of the phenol with elimination of a mole of water (see p. 297). Papademetriu[561] has formulated this green-colored compound as furfurylidenebis-2,4,6-trihydroxybenzene, I (R = R′ = R″ = H), and reports the composition to be independent of the concentrations of phloroglucinol, furfural and hydrochloric acid. He also prepared the related compounds tabulated below by condensing furfural with the mono-, di-, and trimethyl ethers of phloroglucinol. When the last was reacted with 5-(hydroxymethyl)furfural in cold, dilute hydrochloric acid, condensation



I

R	R′	R″	m.p. (°C.)
H	H	H	—
H	H	CH_3	68
H	CH_3	CH_3	167–168
CH_3	CH_3	CH_3	172–174

proceeded all the way to II (m.p. 155°, from alcohol) which was also ob-

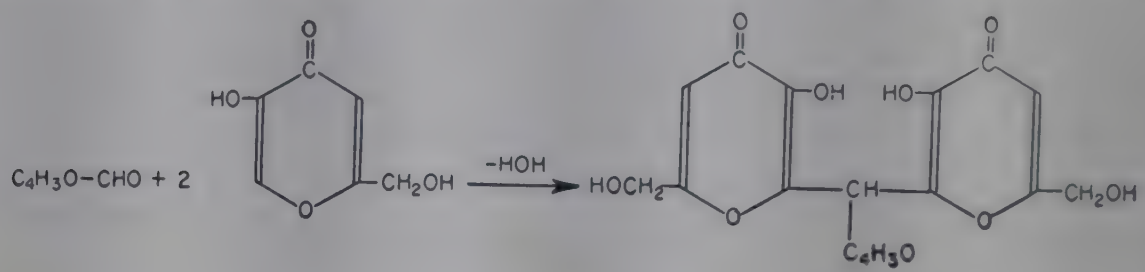


II

[561] Papademetriu, Thesis, University of Leipzig, 1936.

tained by the action of 1,3,5-trimethoxybenzene on oxybis(5-methylenefurfural), the bimolecular ether of 5-(hydroxymethyl)furfural.[561]

Furfural and (hydroxymethyl)furfural condense similarly with α-naphthol as shown by the work of Bredereck[562] who demonstrated that furfurylidenedi-α-naphthols were intermediates responsible for the violet color obtained in the Molisch test for carbohydrates. Also related is the condensation of furfural with kojic acid to form III, m.p. 210–211°.[563]



III

[562] Bredereck, *Ber.*, **64**, 2856 (1931); **65**, 1110 (1932).
[563] Barham and Reed, *J. Am. Chem. Soc.*, **60**, 1541 (1938).

Chapter 10

MISCELLANEOUS ALDEHYDES OF THE FURAN SERIES

Furancarbonals other than Furfural

5-Methylfurfural and Other Alkyl-2-furaldehydes

As furfural is obtained from pentoses, so 5-methylfurfural may be derived from methylpentoses.[1, 2, 3, 4, 5] The latter, however, are relatively scarce in nature, and methylfurfural is more commonly synthesized from sucrose by way of (chloromethyl)furfural (p. 412), which is reduced in the medium of its formation by the action of stannous chloride[6, 7] (see also [8]). Additionally, Reichstein[9] obtained the aldehyde from 2-methylfuran by the Gattermann synthesis; Jones[10] by decarboxylation of 5-methyl-4-carboxyfurfural.

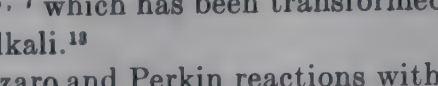
The "fucusole" of Stenhouse[11] (see also p. 274), obtained by distillation of marine plants (*fucus vesiculosus*) with sulfuric acid, was demonstrated to be a mixture of furfural and 5-methylfurfural[12, 1, 13] (see also [14]), and Hill[15, 16] also found both aldehydes in the products obtained on dry distillation (below 200°) of oak. 5-Methylfurfural has also been found in the oil of roasted coffee[17] and in oil of cloves.[18]

5-Methylfurfural: (5-methyl-2-furaldehyde): b.p. 83–84° (15 mm.), 186–187° (760 mm.); d_{18}^{18} 1.107. **Diacetate,** m.p. 25°,[19] **oxime,** *syn*-, m.p. 110–112°; *anti*-, m.p. 51–

[1] Maquenne, *Ann. chim. phys.* (*6*), **22,** 76 (1891).
[2] Günther and Tollens, *Ann.*, **271,** 86 (1892).
[3] Fischer and Liebermann, *Ber.*, **26,** 2415 (1893).
[4] Runde, Scott and Johnson, *J. Am. Chem. Soc.*, **52,** 1284 (1930).
[5] Marshall and Norris, *Biochem. J.*, **31,** 1053, 1289 (1937).
[6] Rinkes, *Rec. trav. chim.*, **49,** 1118 (1930); **52,** 337 (1933); "Organic Syntheses," **14,** p. 62, New York, John Wiley and Sons (1934).
[7] Scott and Johnson, *J. Am. Chem. Soc.*, **54,** 2549 (1932).
[8] Fenton and Gostling, *J. Chem. Soc.*, **79,** 807 (1901).
[9] Reichstein, *Helv. Chim. Acta*, **13,** 345 (1930).
[10] Jones, *J. Chem. Soc.*, **1945,** 116.
[11] Stenhouse, *Phil. Mag.*, **37,** 226 (1850); *Ann.*, **74,** 278 (1850); **163,** 185 (1872).
[12] Maquenne, *Compt. rend.*, **109,** 571, 603 (1889).
[13] Bieler and Tollens, *Ann.*, **258,** 110 (1890).
[14] Oliveri and Peratoner, *Gazz. chim. ital.*, **19,** 635 (1889).
[15] Hill, *Ber.*, **22,** 607 (1889).
[16] Hill and Jennings, *Am. Chem. J.*, **15,** 158 (1893).
[17] Internationale Nahrungs- und Genussmittel A.-G., British Pat. 246,454 (1925); *C. A.*, **21,** 466 (1927); British Pat. 260,960 (1925); *C. A.*, **21,** 3401 (1927).
[18] Masson, *Compt. rend.*, **149,** 795 (1909).
[19] Blanksma, *Chem. Weekblad*, **6,** 717 (1909); *C. A.*, **4,** 752 (1910).

52°[20, 21, 7]; **semicarbazone,** m.p. 197°.[9] Various hydrazones and semioxamazones are known (see Chapter 9). **5-Methylfurfurylidene-β-naphthylamine,** m.p. 87–88°.[22] With ammonia, the aldehyde condenses to form the homolog of hydrofuramide, m.p. 86–87°,[15, 16, 7] which has been transformed into the isomeric furfurin homolog by the action of alkali.[13]

For Cannizzaro and Perkin reactions with the aldehyde, see Scott and Johnson[7] (see also [23]). For Wolff-Kizhner reduction, see Reichstein[9] (see also [24]); catalytic hydrogenation, see [7]. For condensation with methyl ketones, see Alder and Schmidt[25] (see also [26]). For quantitative estimation with barbituric acid, thiobarbituric acid, 2,4-dinitrophenylhydrazine, phloroglucinol, and by bromine titration, see Iddles and French.[27]

3-Methylfurfural:  b.p. 60–61° (12 mm.). **Semicarbazone,** m.p. 216–218° (dec.); **oxime,** m.p. 73–76°; b.p. *ca.* 106° (12 mm.). Obtained by the Gattermann synthesis from 3-methylfuran, and converted to the corresponding nitrile and carboxylic acid.[28]

4,5-Dimethylfurfural: b.p. 87° (11 mm.); by the Gattermann synthesis from 2,3-dimethylfuran. Gives intensive color with aniline-acetic acid reagent.[29]

3,5-Dimethylfurfural: b.p. *ca* 78° (13 mm.). **Semicarbazone,** m.p. 220–221° (dec.). Prepared, as in the preceding example, from 2,4-dimethylfuran.[28]

3,4-Dimethylfurfural: b.p. *ca.* 84° (11 mm.); by the Gattermann synthesis from 3,4-dimethylfuran.[29]

3,4,5-Trimethylfurfural: b.p. 68° (0.3 mm.); m.p. 31–32°; gives deep yellow color with aniline-acetic acid reagent. Obtained from 2,3,4-trimethylfuran by the Gattermann synthesis. Converted to the carboxylic acid by the action of alkaline silver oxide, and also reduced, via the hydrazone, to tetramethylfuran.[30]

5-Ethylfurfural: b.p. 79–81° (12 mm.). **Semicarbazone,** m.p. 176–177°. From 2-ethylfuran by the Gattermann synthesis.[9] For oxidation to corresponding acid, see Reichstein and Zschokke.[31]

5-*i*-Propylfurfural: b.p. 86–87° (11 mm.), 91° (11 mm.); n_D^{25} 1.5085; d_{25}^{25} 1.0330; gives positive color test with aniline-acetic acid reagent. **Semicarbazone,** m.p. 167°, 159°. Obtained from 2-*i*-propylfuran by the Gattermann synthesis[32] and by Rosenmund reduction of 5-*i*-propyl-2-furoyl chloride.[33] For the condensation of the aldehyde

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[20] Meigen, *Ber.*, **40,** 3567 (1907).
[21] Fromherz and Meigen, *Ber.*, **40,** 403 (1907).
[22] Cooper and Nuttall, *J. Chem. Soc.*, **101,** 1074 (1912).
[23] Blanksma, *Chem. Weekblad*, **9,** 186 (1912); *C. A.*, **6,** 1433 (1912).
[24] Yur'ev, Tronova, L'vova and Bukshpan, *J. Gen. Chem. U.S.S.R.*, **11,** 1128 (1941); *C. A.*, **37,** 4071 (1943).
[25] Alder and Schmidt, *Ber.*, **76,** 183 (1943).
[26] Hunsdiecker, *Ber.*, **75,** 447 (1942).
[27] Iddles and French, *Ind. Eng. Chem., Anal. Ed.*, **8,** 283 (1936).
[28] Reichstein, Zschokke and Goerg, *Helv. Chim. Acta*, **14,** 1277 (1931).
[29] Reichstein and Grüssner, *Helv. Chim. Acta*, **16,** 28 (1933).
[30] Reichstein, Zschokke and Syz, *Helv. Chim. Acta*, **15,** 1112 (1932).
[31] Reichstein and Zschokke, *Helv. Chim. Acta*, **15,** 1124 (1932).
[32] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15,** 1118 (1932).
[33] Gilman and Burtner, *J. Am. Chem. Soc.*, **57,** 909 (1935).

with levulinic acid and with sodium succinate and acetic anhydride, see Reichstein and Hirt.[34]

4-*i*-Propylfurfural: b.p. 101–103° (21 mm.); n_D^{25} 1.5041; d_{25}^{25} 1.023. **Semicarbazone,** m.p. 174–176°. Obtained by alkylation of furfural with *i*-propyl chloride in the presence of aluminum chloride[35] (see also [36, 37] and p. 340).

5-*t*-Butylfurfural: b.p. 93–95° (13 mm.); n_D^{25} 1.5001; d_{25}^{25} 1.001; by Friedel-Crafts alkylation of furfural with aluminum chloride, and also by Rosenmund reduction of the corresponding acid chloride.[33]

4-*t*-Butylfurfural: b.p. 93–95° (13 mm.). **Semicarbazone,** m.p. 187°. By Pd-catalyzed hydrogenation of the corresponding acid chloride.[33]

5-*t*-Pentylfurfural: b.p. 95–98° (15 mm.); n_D^{25} 1.4870; d_{25}^{25} 0.9204. **Semicarbazone,** m.p. 196°. Prepared from furfural by Friedel-Crafts alkylation ($AlCl_3$) with *n*-pentyl chloride[33] (see also p. 341).

5-Benzylfurfural: m.p. 30.5–31°. **Phenylhydrazone,** m.p. 199–204°; **phenylbenzylhydrazone,** m.p. 133°; **oxime,** m.p. 99° (*anti*). Derived by the Friedel-Crafts reaction ($AlCl_3$) of 5-(chloromethyl)furfural with benzene.[38, 39] The *syn*-oxime is sweeter than saccharin, and seven times sweeter than the *anti* form.[39, 40]

5-(Tolylmethyl)furfural: $MeC_6H_4CH_2—C{=}CH—CH{=}C—CHO$ (the furan ring closed through O); m.p. 74.5°; from 5-(chloromethyl)furfural and toluene in the presence of aluminum chloride.[38]

Arylfurfurals: These types are said to be produced by the action of aromatic diazonium salts on furfural.[41]

5-(Hydroxymethyl)furfural and Related Compounds

5-(Hydroxymethyl)furfural was discovered by Düll[42] when investigating the action of hot, aqueous oxalic acid on the polysaccharide, inulin. The product was studied further by Kiermeyer[43] who also obtained it by similar treatment of sucrose, and observed that under the conditions employed, the glucose portion of the molecule was largely recoverable. The correct structure was assigned some years later by van Ekenstein and Blanksma,[44, 45, 46] (see also [47, 38, 48]) who drew attention to the fact that many of the

[34] Reichstein and Hirt, *Helv. Chim. Acta*, **16**, 121 (1933).
[35] Gilman, Calloway and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).
[36] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).
[37] Gilman, McCorkle and Calloway, *J. Am. Chem. Soc.*, **56**, 745 (1934).
[38] Fenton and Robinson, *J. Chem. Soc.*, **95**, 1334 (1909).
[39] Gilman and Dickey, *J. Am. Chem. Soc.*, **52**, 2010 (1930).
[40] Gilman, Brown, Dickey, Hewlett and Wright, *Proc. Iowa Acad. Sci.*, **36**, 265 (1929); *C. A.*, **25**, 1245 (1931).
[41] Oda, *Teijin Times*, **19**, No. 4, 7 (1949); *C. A.*, **44**, 5314 (1950).
[42] Düll, *Chem. Ztg.*, **19**, 1003 (1895); *Chem. Centr.*, **1895**, I, 534.
[43] Kiermeyer, *Chem. Ztg.*, **19**, 1003 (1895); *Chem. Centr.*, **1895**, I, 214.
[44] van Ekenstein and Blanksma, *Chem. Weekblad*, **6**, 217 (1909); *Chem. Centr.*, **1909**, I, 1509.
[45] Blanksma, *Chem. Weekblad*, **6**, 1047 (1909); *C. A.*, **5**, 1095 (1911).
[46] van Ekenstein and Blanksma, *Ber.*, **43**, 2355 (1910).
[47] Fenton and Gostling, *J. Chem. Soc.*, **75**, 423 (1899).
[48] Angelico and Coppola, *Gazz. chim. ital.*, **42**, II, 583 (1912).

color reactions of hexoses, earlier ascribed to furfural, were more properly attributable to the formation of (hydroxymethyl)furfural (see [49, 50, 51]).

Düll[42] and Kiermeyer[43] reported (hydroxymethyl)furfural in 20–25 per cent yield from fructose and sorbose. Under the same conditions, glucose, galactose and mannose are attacked only to a very limited extent (see footnote [c], page 408), producing the aldehyde in approximately one per cent yield.[44, 45, 46] Thus, it was recognized early that the ketohexoses are more readily transformed into (hydroxymethyl)furfural than are the aldohexoses. This is clearly demonstrated in the later work of Singh, Dean and Cantor[52] (see also [53]) whose data afford a comparison of glucose and fructose under similar conditions.

In recent years, Haworth and Jones[54] (see also [55, 56, 57, 58]) re-examined the preparation from sucrose, and were able to isolate the crude aldehyde in 54 per cent yield based on the fructose portion of the sugar molecule, or *ca.* 27 per cent based on all twelve carbons. The glucose portion was shown to be, for the most part, unchanged.[a] They proposed the following scheme by way of the enol, A, to account for the conversion of fructose, I (furanose form), and reasoned that the same result might be obtained from glucose, II, if the latter could be made to react in the form of its ene-diol, B, which they assume, could undergo cyclodehydration to give A. To accomplish this, glucose was pretreated with aqueous calcium hydroxide, and then subjected to the action of oxalic acid, whereupon (hydroxymethyl)furfural was obtained in 13 per cent yield[b]; over-all yield about 29 per cent when this dual treatment was repeated four times[54] (see also [60]). Of interest in

[a] Following removal of the (hydroxymethyl)furfural, the residue was oxidized by the action of nitric acid, and saccharic acid was isolated in a yield almost identical to that obtainable on similar oxidation of glucose.[54]

[b] An alternative explanation of Haworth's[54] results is that the preliminary alkali treatment of glucose gave rise to a mixture of glucose, mannose, and fructose (see [59]); that the (hydroxymethyl)furfural subsequently produced by the action of aqueous oxalic acid had its origin in the fructose so formed.

[49] Ville and Derrien, *Compt. rend. soc. biol.*, **66**, 175 (1909); *C. A.*, **3**, 1180 (1909); *Bull. soc. chim.* (*4*), **5**, 895 (1909).

[50] Bredereck, *Ber.*, **65**, 1110 (1932).

[51] Middendorp, *Rec. trav. chim.*, **38**, 1 (1919).

[52] Singh, Dean and Cantor, *J. Am. Chem. Soc.*, **70**, 517 (1948).

[53] Montgomery and Wiggins, *J. Soc. Chem. Ind. London*, **66**, 31 (1947).

[54] Haworth and Jones, *J. Chem. Soc.*, **1944**, 667.

[55] Chandrasena, *J. Chem. Soc.*, **1930**, 2035.

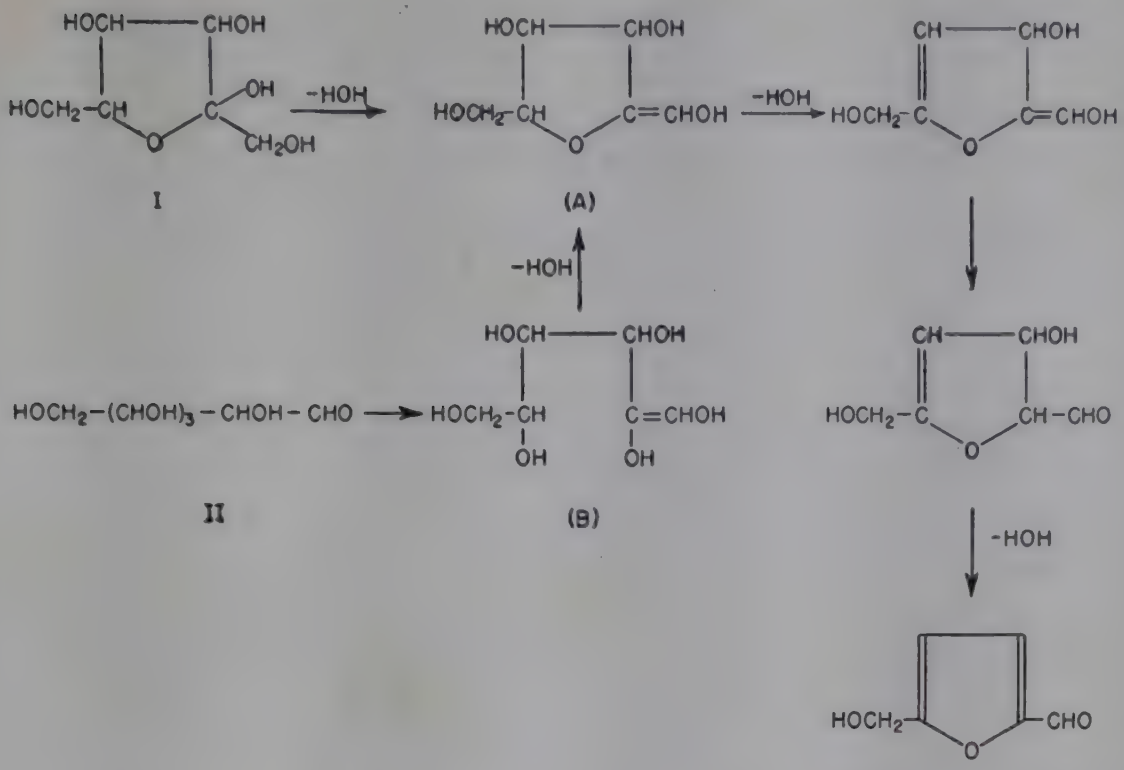
[56] van Kleef, *Rec. trav. chim.*, **51**, 692 (1932).

[57] Haworth and Wiggins, British Pat. 591,858 (1947); *C. A.*, **42**, 1317 (1948); British Pat. 600,871 (1948); *C. A.*, **42**, 7340 (1948); U. S. Pat. 2,498,918 (1950).

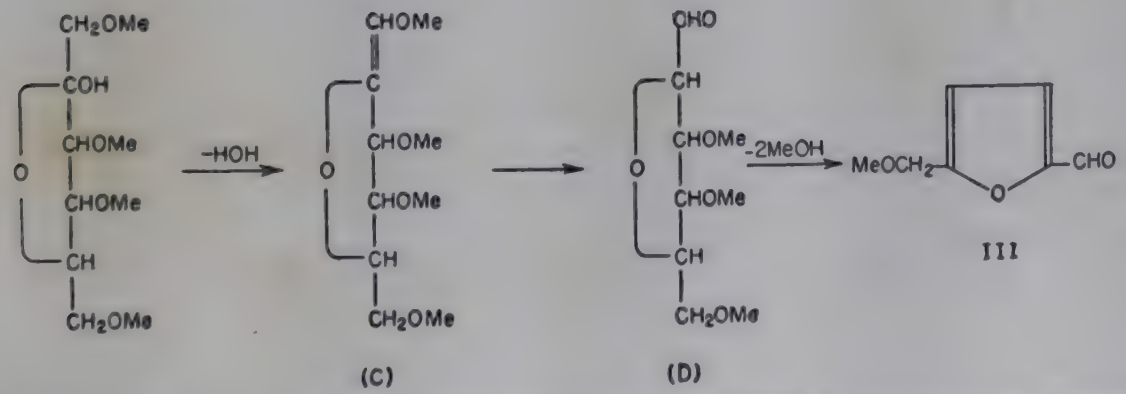
[58] Patton, *J. Dairy Sci.*, **33**, 324 (1950).

[59] Gilman, "Organic Chemistry," Vol. II, p. 1511, New York, John Wiley and Sons (1938).

[60] Braun, *Biokhimiya*, **4**, 276 (1939); *C. A.*, **34**, 1654 (1940).



this same connection is the formation of 5-(methoxymethyl)furfural, III, from tetramethylfructofuranose, which Haworth[61] has formulated in a similar manner, with the enol ether, C, as the key intermediate. Note, however, that he proposes hydrolysis and rearrangement of C to the aldehyde form, D, as the next step. This is most reasonable, in acidic medium, and we believe that the scheme presented above is better interpreted in this way; rearrangement of A to the aldehyde form preceding dehydration. III has also been obtained from tetramethylglucoseen,[62] the proposed mechanism in this case being similar to that illustrated below for the direct conversion of glucose to (hydroxymethyl)furfural by the action of aqueous acids.



[61] Haworth, Hirst and Nicholson, *J. Chem. Soc.*, **1927**, 1513.
[62] Wolfrom, Wallace and Metcalf, *J. Am. Chem. Soc.*, **64**, 265 (1942).

The direct conversion of glucose, IV, without preliminary alkali treatment[63, 53, 52] has been formulated by Wolfrom[64] (see also [65, 66]) in terms of an intermediate enol, E, similar to that described earlier (see p. 290) to account for the formation of furfural from xylose. It is not surprising that little of this reaction occurred in the work of Haworth and Jones.[54] The experimental conditions were too mild to materially affect the glucose.[c] The more rigorous treatment applied by Sowden,[67] whereby glucose was heated with 10 per cent hydrobromic acid for 24 hours at 130°, gave rise to levulinic acid, V, in 48 per cent yield. If, as is generally assumed, the latter has its origin in (hydroxymethyl)furfural (see [43, 46, 68, 69]), it is apparent that in this instance, furanization of glucose occurred to an advanced degree. The other product of degradation was formic acid, and Sowden[67] who used D-glucose-1-C^{14} as the starting material, demonstrated that the aldehyde carbon of the sugar becomes the carbon atom of the formic acid. This work also points up the fact that the yield of (hydroxymethyl)furfural is, in general, a poor criterion of the degree of conversion of the sugar, since the aldehyde is subject to degradative cleavage under the conditions of its formation.

(Hydroxymethyl)furfural has also been obtained, in low yield, directly from cellulose[71] (see also [72, 73]), agar-agar and starch.[74] For its formation,

[c] Saeman[70] (see also [52]) has measured the rates of decomposition of glucose, galactose and mannose in aqueous, acidic medium, and has demonstrated that these aldohexoses are considerably more stable than xylose. Extrapolation of Saeman's data, assuming that the K_{ion} of oxalic acid at 25° remains relatively unaltered by increase in temperature, indicates that under the conditions employed by Haworth and Jones[54] for the conversion of sucrose, only about one per cent of the glucose portion of the molecule would be decomposed.

[63] Scallet and Gardner, *J. Am. Chem. Soc.*, **67**, 1934 (1945).

[64] Wolfrom, Schuetz and Cavalieri, *J. Am. Chem. Soc.*, **70**, 514 (1948).

[65] Hurd and Isenhour, *J. Am. Chem. Soc.*, **54**, 317 (1932).

[66] Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944).

[67] Sowden, *J. Am. Chem. Soc.*, **71**, 3568 (1949).

[68] Pummerer and Gump, *Ber.*, **56**, 999 (1923); Pummerer, Guyot and Birkofer, *Ber.*, **68**, 480 (1935).

[69] Teunissen, *Rec. trav. chim.*, **49**, 784 (1930); **50**, 1 (1931).

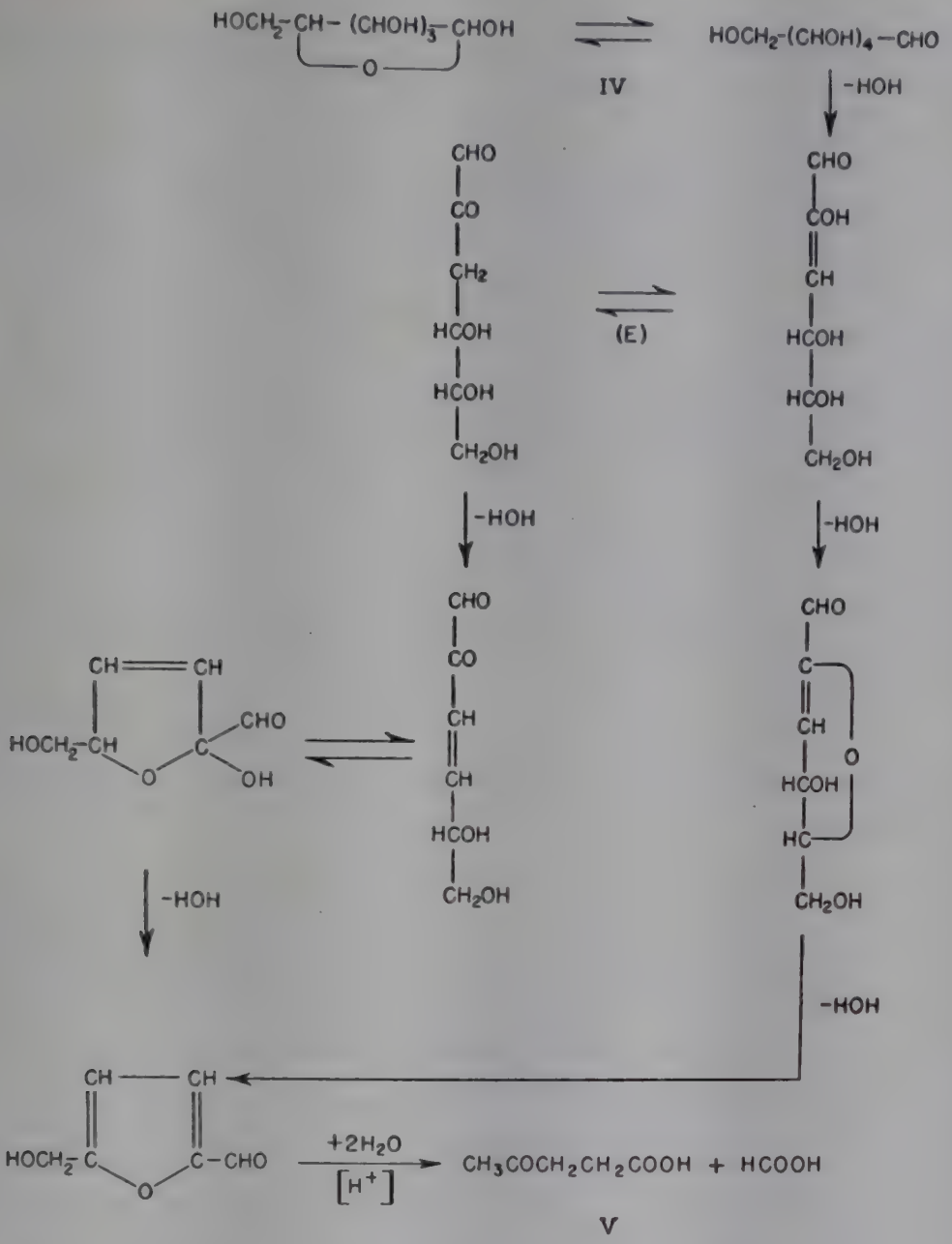
[70] Saeman, *Ind. Eng. Chem.*, **37**, 43 (1945).

[71] Heuser and Eisenring, *Cellulosechemie*, **4**, 25 (1923); *C. A.*, **17**, 3249 (1923).

[72] Erdmann, *Ber.*, **43**, 2391 (1910).

[73] Hess, "Die Chemie der Zellulose und Ihrer Begleiter," p. 490, Leipzig, Akademische Verlagsgesellschaft m.b.H.(1928).

[74] Aso, *J. Agr. Chem. Soc. Japan*, **10**, 1201 (1934); *C. A.*, **29**, 1088 (1935).



along with furfuryl alcohol in heated skim milk, see Patton[58] who also isolated the aldehyde in trace amounts by heating β-lactose with glycine and with sodium caseinate. Other carbohydrate sources include chitose,[45] methyl 3,6-anhydro-α-D-galactoside[75] and methyl α-D-glucoside.[52] Additionally, it has been prepared by hydrolysis of 5-(bromomethyl)- and 5-(chloromethyl)furfurals.[47, 76, 39] For the occurrence of (hydroxymethyl)furfural

[75] Araki and Arai, *J. Chem. Soc. Japan*, **63**, 1522 (1942); *C. A.*, **41**, 3062 (1947).
[76] Cooper and Nuttall, *J. Chem. Soc.*, **99**, 1193 (1911).

in wines, see Amerine,[77] Cunha,[78] Kruisheer, Vorstman and Kniphorst,[79] Torricelli[80] and Yamada[81]; in honey, see Fiehe and Kordatzki,[82] Mohler,[83] Troje[84] and Weiss.[85]

5-(Bromomethyl)- and 5-(chloromethyl)furfural have been known almost as long as the hydroxymethyl aldehyde. They were first prepared by Fenton and Gostling[47, 86, 8] (see also [38, 72, 76]) by the action of ethereal hydrogen bromide or chloride on hexoses; most readily from fructose. Later, Fischer and Neyman[87] (see also [51]) synthesized (chloromethyl)furfural from sucrose using fuming hydrochloric acid (d 1.19), and more recently, Haworth and Jones[54] have reported this product in 21 per cent yield (based on the sucrose molecule) by passing hydrogen chloride through a suspension of aqueous sucrose in carbon tetrachloride. The (halomethyl)furfurals have also been obtained by the action of hydrogen bromide[88] (see also [51]) and hydrogen chloride[89] on an ethereal solution of (hydroxymethyl)furfural. Using one per cent alcoholic hydrogen chloride, sucrose,[90] glucose,[91] and fructose or inulin[92, 93] give rise to a mixture of levulinic esters and the appropriate 5-(alkoxymethyl)furfural, the latter also being obtainable from the halomethyl aldehydes by treatment with the desired alcohol in the presence of barium carbonate.[76, 87, 51]

5-(Hydroxymethyl)furfural: (5-hydroxymethyl-2-furaldehyde): m.p. 31.5°; b.p. 110° (0.02 mm.); n_D^{18} 1.5627[54]; soluble in water, alcohol, acetone, ether, chloroform and benzene. In contrast with furfural, it is very little volatile with steam.[51] **Oxime,** *syn-*, m.p. 108°; *anti-*, m.p. 77–78°[43]; **aldazine,** m.p. 168°; $+2H_2O$, m.p. 174°.[51] Various

[77] Amerine, *Wines and Vines*, **28**, No. 3, 23, 42 (1947); *C. A.*, **41**, 6367 (1947); *Food Research*, **13**, 264 (1948); *C. A.*, **42**, 7928 (1948).

[78] Cunha, *Anais inst. vinho Porto*, **1947**, 51; *C. A.*, **43**, 3559 (1949).

[79] Kruisheer, Vorstman and Kniphorst, *Z. Untersuch. Lebensm.*, **69**, 570 (1935); *C. A.*, **29**, 7575 (1935).

[80] Torricelli, *Mitt. Lebensm. Hyg.*, **37**, 181 (1946); *C. A.*, **41**, 816 (1947).

[81] Yamada, *Bull. Chem. Soc. Japan.* **4**, 31 (1929); *C. A.*, **23**, 2781 (1929).

[82] Fiehe and Kordatzki, *Z. Untersuch. Lebensm.*, **56**, 490 (1928); *C. A.*, **23**, 3030 (1929); *Ibid.*, **57**, 468 (1929); *C. A.*, **24**, 666 (1930); *Ibid.*, **58**, 69 (1929); *C. A.*, **24**, 898 (1930).

[83] Mohler, *Mitt. Lebensm. Hyg.*, **32**, 230 (1941); *C. A.*, **37**, 3195 (1943).

[84] Troje, *Z. Ver. deut. Zucker-Ind.*, **75**, 635 (1925); *C. A.*, **20**, 3753 (1926).

[85] Weiss, *Z. Untersuch. Lebensm.*, **58**, 320 (1929); *C. A.*, **24**, 1908 (1930).

[86] Fenton and Gostling, *J. Chem. Soc.*, **79**, 361 (1901).

[87] Fischer and Neyman, *Ber.*, **47**, 973 (1914).

[88] Newth and Wiggins, *J. Chem. Soc.*, **1947**, 396.

[89] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 249 (1932).

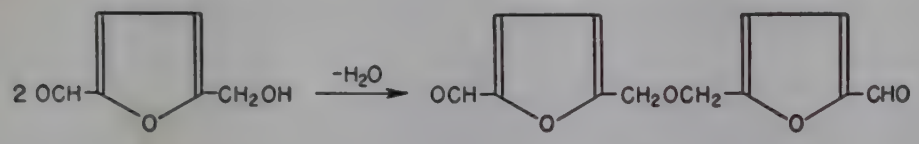
[90] Weidenhagen and Korotkyj, *Z. Wirtschaftsgruppe Zuckerind.*, **85**, 131 (1935); *C. A.*, **29**, 7325 (1935).

[91] Spengler, Weidenhagen and Korotkyj, German Pat. 635,783 (1936); *C. A.*, **31**, 1041 (1937).

[92] Weidenhagen and Korotkyj, *Z. Ver. deut. Zucker-Ind.*, **84**, 470 (1934); *C. A.*, **29**, 4760 (1935).

[93] Spengler, Weidenhagen and Korotkyj, German Pat. 632,322 (1936); *C. A.*, **30**, 6761 (1936).

substituted hydrazones and semioxamazones (see pp. 364, 370). **Semicarbazone,** m.p. 192°[94, 54]; **urethans:** *p*-nitrophenyl, m.p. 187°[95]; 2,4-dinitrophenyl, m.p. 156°.[96] The aldehyde condenses with two moles of urea to give a **diureide,** m.p. 164°. Similarly, with the appropriate amide there is obtained **N,N'-5-(hydroxymethyl)furfurylidenediacetamide,** m.p. 206°, and **dibenzamide,** m.p. 180°.[97] **5-(Hydroxymethyl)furfurylidene-β-naphthylamine,** m.p. 131–132°.[22] For color reaction (Dische reaction) with diphenylamine-(acetic acid)-(sulfuric acid) reagent, see Deriaz, Stacey, Teece and Wiggins.[98] For attempted conversion to products related to hydrofuramide and furoin, see Middendorp.[51] For Perkin reaction, see Karashima[99]; condensation with malonic acid and ester, see Middendorp.[51] For reduction by Wolff-Kizhner method, see Reichstein and Zschokke[89]; catalytic hydrogenation, see Newth and Wiggins.[98a] The Cannizzaro reaction was successfully carried out by Blanksma[94] (see also [51]). When heated,[d] (hydroxymethyl)furfural condenses with loss of water to form **oxybis(5-methylenefurfural),** VI, m.p. 112° (dioxime, m.p. 167–168°; bissemicarbazone, m.p. 255°[51, 100, 88]) which explains why this product is generally formed along with (hydroxymethyl)furfural when the latter is prepared by the action of aqueous acids on hexoses. The dicarboxylic acid corresponding to VI is described elsewhere (p. 558). Condensation of VI with aniline and pyruvic acid



VI

(Doebner reaction) produces the expected **oxybis[2-(5-methylene-2-furyl)cinchoninic acid],** m.p. 251°.[101] For the condensation of VI with malonylurea, see Iseki[102] (see also [103]). (Hydroxymethyl)furfural is readily decomposed by aqueous acids (Kiermeyer[43] (see also [104])), cleavage resulting in the formation of levulinic and formic acids. Teunissen[69] showed that in dilute aqueous medium this reaction follows a first order mechanism, and this has been confirmed in recent years.[52] The mechanism of this reaction is considered elsewhere (see Chapter 14).

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[d] By repeated distillation at atmospheric pressure, (hydroxymethyl)furfural is reported to undergo partial conversion to furfural.[51, 81] Presumably formaldehyde is the other product of degradation, although Middendorp[51] failed to detect it in his study of the decomposition.

[94] Blanksma, *Rec. trav. chim.*, **29,** 403 (1910).

[95] van Hoogstraten, *Rec. trav. chim.*, **51,** 414 (1932).

[96] van Ginkel, *Rec. trav. chim.*, **61,** 149 (1942).

[97] Karashima, *Z. physiol. Chem.*, **184,** 268 (1929); *C. A.*, **24,** 362 (1930).

[98] Deriaz, Stacey, Teece and Wiggins, *J. Chem. Soc.*, **1949,** 1222.

[98a] Newth and Wiggins, *Research London*, **3,** Suppl., 50 (1950); *C. A.*, **44,** 6848 (1950).

[99] Karashima, *Z. physiol. Chem.*, **180,** 241 (1929); *C. A.*, **23,** 2175 (1929).

[100] Iseki, *Z. physiol. Chem.*, **216,** 130 (1933); *C. A.*, **27,** 2953 (1933); Iseki and Sugiura, *J. Biochem. Japan*, **30,** 113 (1939); *C. A.*, **34,** 2370 (1940).

[101] Iseki and Sugiura, *J. Biochem. Japan*, **30,** 119 (1939); *C. A.*, **34,** 2366 (1940).

[102] Iseki, *J. Biochem. Japan*, **19,** 7 (1934); *C. A.*, **28,** 2709 (1934).

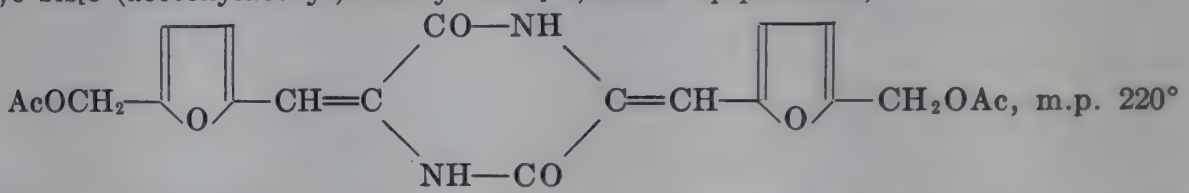
[103] Iseki, *Z. physiol. Chem.*, **216,** 127 (1933); *C. A.*, **27,** 2953 (1933).

[104] Blanksma and Egmond, *Rec. trav. chim.* **65,** 309 (1946).

5-(Chloromethyl)furfural: m.p. 37–38°; b.p. *ca.* 90° (1 mm.). **Phenylhydrazone,** m.p. 118–120°.[8, 87, 51, 105, 39, 89, 54] The aldehyde is an irritant to the skin.[106] Reduction with stannous chloride in hydrochloric acid gives rise to 5-methylfurfural[8] (see also p. 403). Careful oxidation with nitric acid produces 2,5-furandicarbonal, OCH—C=CHCH=C—CHO, m.p. 109.5–110°; dioxime, m.p. 212.5–213°[22] (see also p. 635).

5-(Bromomethyl)furfural: m.p. 59.5–60.5°, 61°.[47, 86, 72, 51, 88] For discussion of crystal structure, see Lewis.[107] For comparative yields from a variety of carbohydrates, see Hibbert and Hill.[108] For color reaction with primary aromatic amines in acetic acid, see Fenton.[109] With silver in boiling benzene, coupling occurs with formation of 5,5′-ethylenedifurfural[8, 88] (see also p. 414).

5-(Acetoxymethyl)furfural: m.p. 55°; by the action of silver acetate on 5-(chloromethyl)furfural.[8] **2,4,6-Trinitrophenylhydrazone,** two forms, m.p. 205–207° and 198–199°.[110] Condensation with 2,5-diketopiperazine (glycine anhydride) gives rise to 3,6-bis[5-(acetoxymethyl)furfurylidene]-2,5-diketopiperazine,



(dec.).[97] **5-(Acetoxymethyl)furfurylidene diacetate,** m.p. 73°, is obtained by treating 5-(hydroxymethyl)furfural with acetic anhydride and a trace of concentrated sulfuric acid[19] (see also [99]).

5-(Benzoxymethyl)furfural: m.p. 56–57°; from (chloromethyl)furfural[8] and by the action of benzoyl chloride (Schotten-Baumann reaction) on (hydroxymethyl)furfural. **Oxime,** m.p. 85–85.5°; **aldazine,** m.p. 163°; **phenylhydrazone,** m.p. 112°; **p-nitrophenylhydrazone,** m.p. 142°; **semicarbazone,** m.p. 198°; **semioxamazone,** m.p. 204° (dec.).[51]

5-(Methoxymethyl)furfural: m.p. −8°, −9°; b.p. 53° (0.05 mm.), 68–70° (2 mm.); $d_D^{17.9}$ 1.146; $n_D^{19.6}$ 1.5088.[51, 61, 62] **Oxime,** m.p. 97–98° (uncorr.), 103–104°[62, 61]; **phenylhydrazone,** m.p. 56–57°; **p-nitrophenylhydrazone,** m.p. 140–141°[51]; **2,4-dinitrophenylhydrazone,** two forms, red, m.p. 183–184°; yellow, m.p. 137–138°[112]; **2,4,6-trinitrophenylhydrazone,** two forms, m.p. 180–182° and 165–167°[110]; **aldazine,** m.p. 86°[51]; **semicarbazone,** m.p. 163.5–164.5°, 166–167°, 170°[62, 61, 51]; **semioxamazone,** m.p. 209–210°.[51]

For behavior in the Cannizzaro reaction and for the attempted preparation of the product corresponding to hydrofuramide, see Middendorp.[51]

5-(Ethoxymethyl)furfural: m.p. 9.5–10°; b.p. 75–77° (2 mm.), 119.5° (27 mm.), 235–240°(—); d_{20}^{20} 1.0990; n_D^{20} 1.5097.[105, 51, 76] **Diethyl acetal,** b.p. 131° (25 mm.); d_{20}^{20} 1.0053; n_D^{20} 1.4543[105, 87]; **phenylhydrazone,** m.p. 55.5–56.2°[76, 51]; ***p*-bromophenylhydrazone,** m.p. 104–105°[76]; ***o*-nitrophenylhydrazone,** m.p. 127–129°[110]; ***p*-nitrophenylhydrazone,** m.p. 140–141°[51]; **2,4-dinitrophenylhydrazone,** two forms, red, m.p. 208–

[105] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany' 1930.
[106] Gilman, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **6**, 137 (1932).
[107] Lewis, *J. Chem. Soc.*, **75**, 426 (1899).
[108] Hibbert and Hill, *J. Am. Chem. Soc.*, **45**, 176 (1923).
[109] Fenton, *J. Chem. Soc.*, **83**, 189 (1903).
[110] Bredereck and Fritzsche, *Ber.*, **70**, 802 (1937).

210°; yellow, m.p. 160–161°[112]; **2,4,6-trinitrophenylhydrazone,** two forms, m.p. 176–178° and 152–154°[110]; **aldazine,** m.p. 70°[51]; **semicarbazone,** m.p. 169–170°[87, 51]; **semioxamazone,** m.p. 212–213°.[51]

With aqueous potassium cyanide in alcohol the appropriate furoin, $EtOCH_2-C=CHCH=C-CO-CHOH-C=CHCH=C-CH_2OEt$ (O), m.p. 82°, is produced in 20 per cent yield.[105] For conversion to 2-hydroxymethyl-5-hydroxypyridine, see Aso[113].

5-(*i*-Propoxymethyl)furfural: b.p. 117–120° (12 mm.). **Semicarbazone,** m.p. 188–189°.[90]

5-(s-Butoxymethyl)furfural: b.p. 93–125° (0.13–0.55 mm.). **Semicarbazone,** m.p. 169–170°.[90]

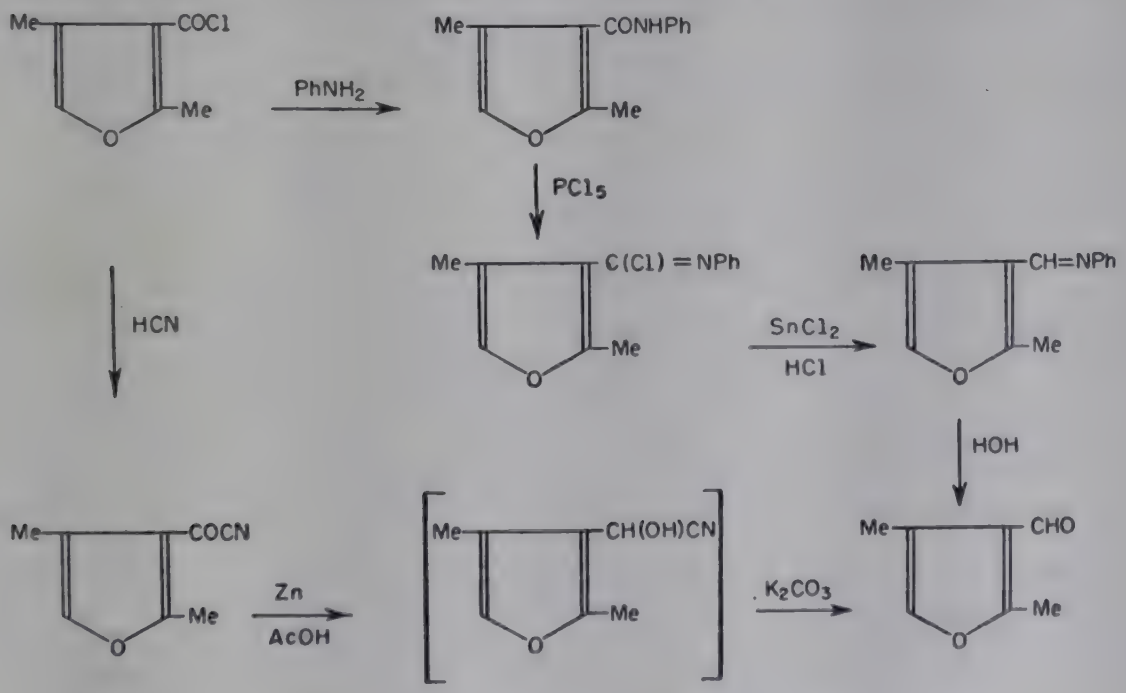
5-(Triphenylmethoxymethyl)furfural: $(C_6H_5)_3C-OCH_2-C=CHCH=C-CHO$ (O); no constants. **2,4-Dinitrophenylhydrazone,** two forms, red, m.p. 246–248°; yellow, m.p. 212–215°.[112]

3-Furaldehydes

3-Furaldehyde: b.p. 66–68° (39 mm.), 144° (732 mm.); n_D^{20} 1.4945; d_{20}^{20} 1.111. **Diacetate,** m.p. 46–47°, 50°; b.p. 118–119° (15 mm.); **phenylhydrazone,** m.p. 149.5°; **semicarbazone,** m.p. 210–211°. Prepared by Pd-catalyzed hydrogenation of 3-furoyl chloride.[114, 115, 116] Unlike furfural, it gives no color test with aniline-(acetic acid) reagent. For reaction with the Grignard reagent, see Yur'ev and Gragerov.[117]

4-Methyl-3-furaldehyde: b.p. 55° (11 mm.). **Hydrazone,** m.p. 44–45°; **semicarbazone,** m.p. 217–218° (dec). By Pd-catalyzed hydrogenation of 4-methyl-3-furoyl chloride. The hydrazone was treated with sodium methoxide (Wolff-Kizhner) for the preparation of 3,4-dimethylfuran.[29]

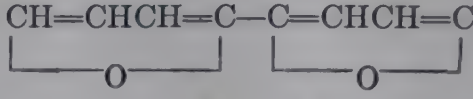
2,4-Dimethyl-3-furaldehyde: b.p. 72–73° (11 mm.). **Oxime,** m.p. 74–76°; **semicarbazone,** m.p. 168°. Prepared from 2,4-dimethyl-3-furoyl chloride by the two routes indicated below.[118] The aldehyde gives no color test with aniline-(acetic acid) re-

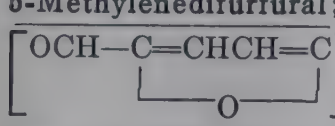


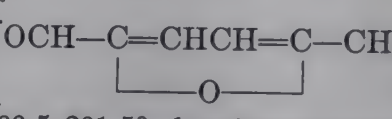
agent.[114] With hydrazine hydrate it gives a **hydrazone,** m.p. 52° (crude), which is converted into 2,3,4-trimethylfuran by the action of sodium methoxide.[30]

2,5-Diphenyl-3-furaldehyde: m.p. 90–92°. **Oxime,** m.p. 171–173°. Obtained by an interesting deamination and cyclization of *cis*-dibenzoyl(morpholinomethyl)ethylene when dissolved in methanolic hydrogen chloride.[119] Reduced to the corresponding alcohol by the action of aluminum isopropoxide.

Aldehydes Containing Two Furan Nuclei

5-(2-Furyl)furfural:  m.p. 54°; b.p. 91–94° (0.4 mm.). **Semicarbazone,** m.p. 221°. By Gattermann reaction from difuryl.[120] Excess reagent failed to introduce another aldehyde group (see p. 69).

5-Methylenedifurfural; (5-methylenedi-2-furaldehyde):  m.p. 118–119°; b.p. *ca.* 165° (0.05 mm.). **Dioxime,** m.p. 185–187° (dec.); **disemicarbazone,** m.p. 260° (dec.); by Gattermann reaction from difurylmethane.[120]

5-Ethylenedifurfural:  m.p. 119.5–121°; b.p. 160° (1 mm.). **Dioxime,** m.p. 200.5–201.5°; **bisphenylhydrazone,** m.p. 179–181°. Obtained by Gattermann reaction from *sym*-difurylethane[9] and from 5-(bromomethyl)furfural by the action of silver in boiling benzene.[8, 88]

Furylalkanals

Furylacetaldehyde; (2-furylethanal); $C_4H_3O—CH_2CHO$; b.p. *ca.* 58° (10 mm.), 140–146° (15 mm.). **Oxime,** *syn*-, m.p. 63–64° (unstable); *anti*-, less stable; **semicarbazone,** m.p. 131–132°. Obtained by decomposition of 3-(2-furyl)glycidic acid (p. 597) with aqueous oxalic[121] and tartaric acids[122] (see also [123]); by reduction of ω-nitrovinylfuran (p. 167) with zinc in acetic acid[124, 4] with aluminum amalgam.[125] Also prepared by the action of sodium hypochlorite on 3-(2-furyl)acrylamide, followed by hydrolysis with dilute sulfuric acid.[126]

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[112] Bredereck, *Ber.*, **65,** 1833 (1932).
[113] Aso, *J. Agr. Chem. Soc., Japan,* **16,** 249 (1940); *C. A.*, **34,** 6278 (1940).
[114] Gilman and Burtner, *J. Am. Chem. Soc.*, **54,** 3014 (1932).
[115] Gilman and Burtner, *J. Am. Chem. Soc.*, **55,** 2903 (1933).
[116] Hayes, *J. Am. Soc.*, **71,** 2581 (1949).
[117] Yur'ev and Gragerov, *Zhur. Obshchei Khim. J. Gen. Chem.*, **19,** 724 (1949); *C. A.*, **44,** 1092 (1950).
[118] Reichstein and Zschokke, *Helv. Chim. Acta,* **15,** 1105 (1932).
[119] Bailey and Lutz, *J. Am. Chem. Soc.*, **67,** 2232 (1945).
[120] Reichstein, Grüssner and Zschokke, *Helv. Chim. Acta,* **15,** 1066 (1932).
[121] Reichstein, *Ber.*, **63,** 749 (1930).
[122] Scheibler and Tutundzitsch, *Ber.*, **64,** 2916 (1931).
[123] Asahina and Fujita, *J. Pharm. Soc. Japan,* **490,** 1084 (1922); *C. A.*, **17,** 2578 (1923).
[124] Bouveault and Wahl, *Bull. soc. chim. (3),* **29,** 521 (1903).
[125] Yabuta and Kambe, *Proc. Imp. Acad. Tokyo,* **4,** 120 (1928); *C. A.*, **22,** 4503 (1928).
[126] Rinkes, *Rec. trav. chim.*, **39,** 200 (1920).

3-(2-Furyl)propionaldehyde: $C_4H_3O—CH_2CH_2CHO$; b.p. 59–61° (4 mm.), 81°, (17 mm.), 179–180° (740 mm.); n_D^{19} 1.4772, n_D^{20} 1.4782, n_D^{25} 1.4470; d_4^{19} 1.0574, d_4^{25} 1.0690. **Semicarbazone**, m.p. 82–83°; **dimethyl acetal**, b.p. 77° (4 mm.); n_D^{20} 1.4550. First obtained by Wienhaus and Leonhardi[127] by hydrogenation of 3-(2-furyl)acrolein. Later, Burdick and Adkins[128] prepared it similarly, in 46 per cent yield, using Raney nickel catalyst. Yet another synthesis has been employed, namely, condensation of furan with acrolein under the influence of sulfur dioxide[129] (see also p. 63).

5-Methyl-2-furylacetaldehyde: $CH_3—C=CHCH=C—CH_2CHO$ (O bridge). **Oxime** (no constants) prepared by reduction of 5-methyl-2-(2-nitrovinyl)furan as an intermediate in the synthesis of 5-methyl-2-furylacetic acid.[7]

3-(5-Methyl-2-furyl)butyraldehyde: $CH_3—C=CHCH=C—CH(CH_3)CH_2CHO$ (O bridge); b.p. 88° (14 mm.). **2,4-Dinitrophenylhydrazone**, m.p. 98°. By condensation of 2-methylfuran with crotonaldehyde under the influence of a few drops of *p*-toluenesulfinic ester.[25]

2,5-Furandipropionaldehyde: $OCH(CH_2)_2—C=CHCH=C—(CH_2)_2CHO$ (O bridge); m.p. 41.2°. **Dioxime**, m.p. 132–133°. Formed along with 3-(2-furyl)propionaldehyde (above) when furan is condensed with an excess of acrolein.[129]

Furylalkenals

Furfural undergoes the aldol condensation with aliphatic aldehydes in alkaline medium, although in only a few isolated instances (p. 334) have the aldols themselves been isolated. Under the conditions of their formation, they generally lose the elements of water to give α,β-unsaturated aldehydes, I (Table 1), which are reported to be of interest for their optical properties, and in perfumery.[130]

$$C_4H_3O—CHO + RCH_2CHO \xrightarrow{\text{aq. NaOH}} [C_4H_3O—CHOH—CHR—CHO]$$

$$\downarrow -HOH$$

$$C_4H_3O—CH=CR—CHO$$

I

Thus, furfural and acetaldehyde in aqueous sodium hydroxide give rise to 3-(2-furyl)acrolein, II ($n = 1$), although the reaction may proceed further if conditions permit. For example, the latter product may condense with acetaldehyde to give 5-(2-furyl)-2,4-pentadienal, II ($n = 2$), which in turn, can react with yet another mole of acetaldehyde with formation of

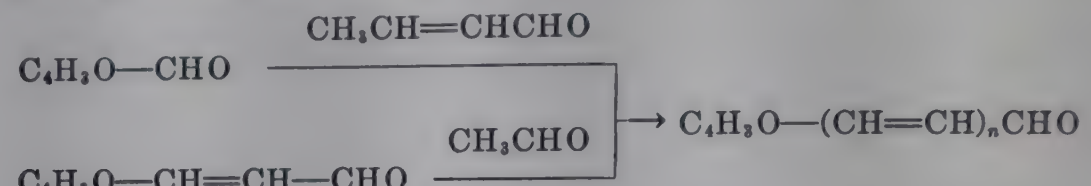
[127] Wienhaus and Leonhardi, *Ber. Schimmel and Co., Akt.-Ges.*, **1929**, 225; *C. A.*, **24**, 2127 (1930).

[128] Burdick and Adkins, *J. Am. Chem. Soc.*, **56**, 438 (1934).

[129] Sherlin, Berlin, Serebrennikova and Rabinovich, *J. Gen. Chem. U.S.S.R.*, **8**, 7 (1938); *C. A.*, **32**, 5397 (1938).

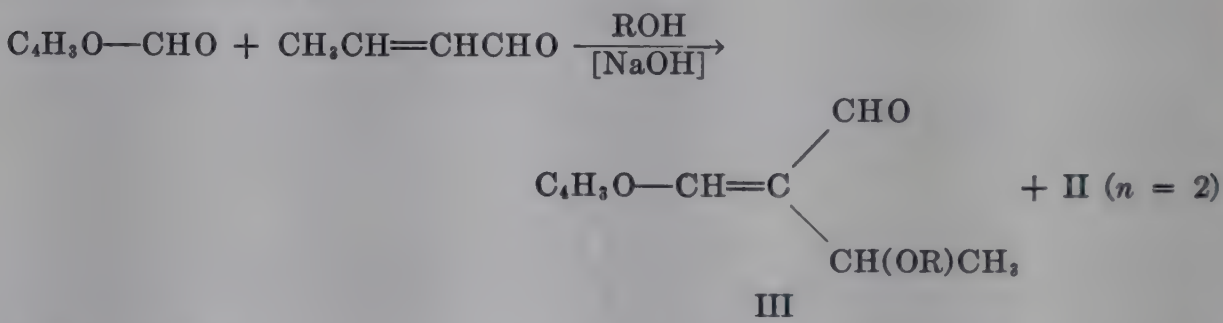
[130] Brunel, French Pat. 844,182 (1939); *C. A.*, **34**, 7296 (1940).

7-furyl-2,4,6-heptatrienal, II (n = 3), and so on. A vinylogous series of these alkenals possessing a terminal furyl group (II, n = 2, 3 ··· 7) (see Table 2) has been prepared by condensing furfural, or II (n = 1, 2 ··· 5), with acetaldehyde, or crotonaldehyde by means of piperidinium acetate,[131] or aqueous sodium hydroxide.[132, 133]



II

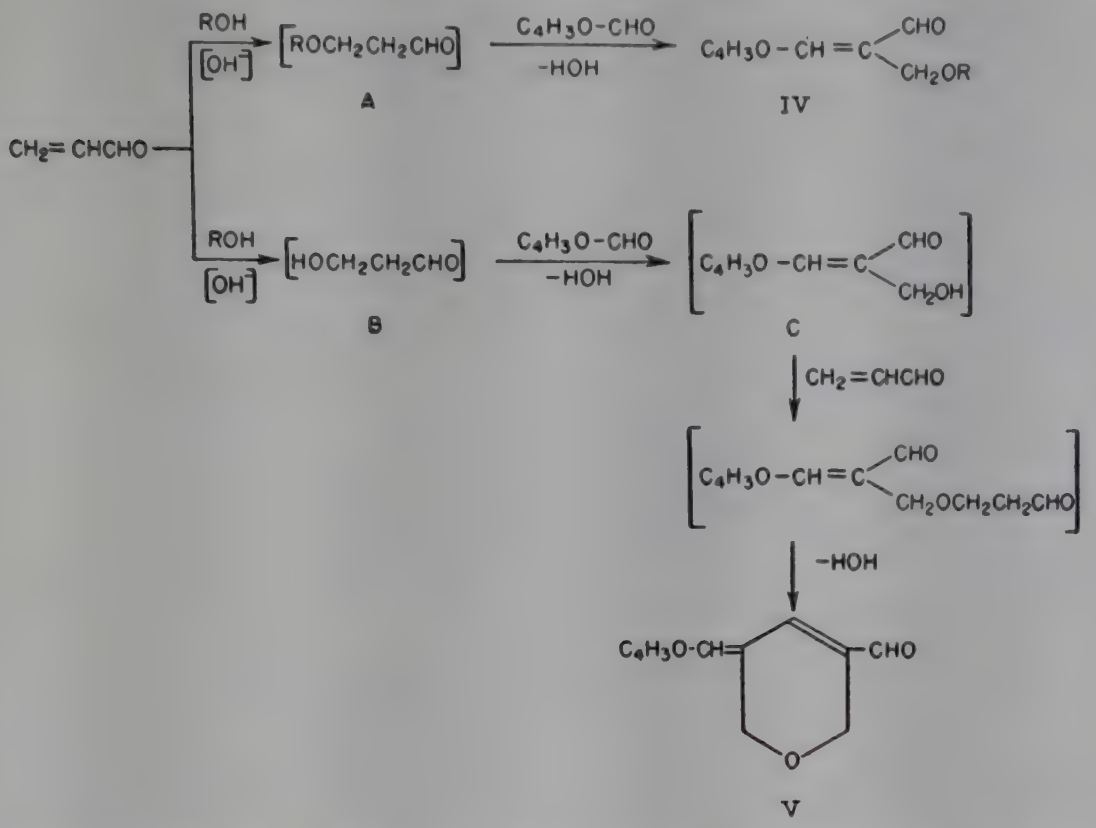
Furylpentadienal (II, n = 2) is obtainable directly from furfural and crotonaldehyde, but when the condensation is carried out in aqueous alkali, 2-(1-hydroxyethyl)-3-(2-furyl)acrolein, III (R = H) is also formed (Table 1). In alcoholic sodium hydroxide, the appropriate ethers, III (Table 1) are the accompanying products.[134]



III

A similar result has been observed when furfural is condensed with acrolein by means of sodium hydroxide. In alcoholic medium, 2-alkoxymethyl-3-(2-furyl)acroleins, IV (see Table 1) are obtained. Hinz and Laberenz[134] explain the reaction in terms of the intermediate formation of ethers, A, of 3-hydroxypropionaldehyde, B, subsequent condensation of furfural with A giving rise to IV. In this instance, however, when the reaction was conducted in aqueous alkali, they were unable to isolate the hydroxy aldehyde C (IV, R = H) (compare III, R = H, which was isolable in the experiment with crotonaldehyde). Instead, condensation proceeded further with an additional molecular equivalent of acrolein, and subsequent cyclodehydration produced the dihydropyran derivative, V, m.p. 109° (phenylhydrazone, m.p. 195°; semicarbazone, m.p. 254°). Vinylogs of III and IV (R = CH_3) have been prepared by condensing furylacrolein with acrolein, and with crotonaldehyde, in methanolic sodium hydroxide (see Table 2).

[131] Schmitt, *Ann.*, **547**, 270 (1941); *C. A.*, **36**, 6523 (1942).
[132] König, *Ber.*, **58**, 2559 (1925).
[133] Hinz, Meyer and Schücking, *Ber.*, **76**, 676 (1943).
[134] Hinz and Laberenz, "On Some Furan Derivatives and Their Catalytic Hydrogenation," PB No. **19416**, U. S. Dept. Commerce, 1944.



3-(2-Furyl)acrolein: m.p. 51–52°; b.p. 94–95° (9 mm.); reported in 88 per cent yield by condensation of furfural with acetaldehyde in dilute, aqueous sodium hydroxide at 0°[133] (see also [141, 142, 135, 132, 143, 144, 128, 139, 145]). **Oxime,** m.p. 110–111°[135, 144]; **aldazine,** m.p. 167–168°[133]; **phenylhydrazone,** m.p. 132°[146]; **semicarbazone,** m.p. 219.5°.[135, 142]

Similar to the behavior of furfural (p. 351), reaction with aromatic amine salts leads to rupture of the furan ring (see Chapter 14) and formation of dyestuffs.[146] With aniline hydrochloride (Shear's reagent) it gives a blue-green color as does the oxime.[147] With amines in the absence of acids, the appropriate aldimines are produced.[148]

Amine	Aldimine m.p. (°C.)
Aniline	65.5
p-Toluidine	74.5–75
3,4-Dimethylaniline	49.5–50
2,4,6-Trimethylaniline	77–77.5
o-Anisidine	77.5–78
p-Anisidine	66
p-Phenylenediamine	188
Benzidine	197–198 (dec.)

[135] Ivanov, *Bull. soc. chim.* (*4*), **35,** 1658 (1924).

[136] Schmidt, *Ber.*, **14,** 574 (1881).

[137] Gutzatz, Russian Pat. 39,763 (1934); *C. A.*, **30,** 3591 (1936).

[138] Ueno, Komori and Terashima, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **52,** 142 (1949); *C. A.*, **45,** 2150 (1951).

[139] Hinz and Meyer, "Degradation Reactions of Hydrogenated Furfural Condensation Products," PB No. **52009,** U. S. Dept. Commerce, 1941; *C. A.*, **41,** 5124 (1947).

[140] Maxim and Popescu, *Bull. soc. chim.* (*5*), **5,** 49 (1938).

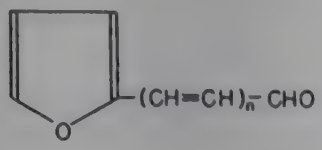
[140a] Ponomarev, Til and Zelenkova, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20,** 1085 (1950); *C. A.*, **44,** 9403 (1950).

TABLE 1. COMPOUNDS RELATED TO 3-(2-FURYL)ACROLEIN

Compound	Physical constants (°C.) and derivatives	Ref.
2-Alkyl-3-(2-furyl)acroleins		
2-Methyl-	b.p. 100 (11 mm.), 227–228 (atm.) $d_4^{13.5}$ 1.1022; $n_D^{13.5}$ 1.613 oxime, m.p. 108–109 semicarbazone, m.p. 250.5–251.5	135; see also 136
2-Ethyl-	b.p. 112–113 (14 mm.), 234–235 (atm.) d_4^{16} 1.065; n_D^{16} 1.595 oxime, m.p. 67–68 aldazine, m.p. 120 phenylhydrazone, m.p. 97–97.5, 109–110 semicarbazone, m.p. 220–221	135, 133
2-*n*-Propyl-	b.p. 120–121 (14 mm.), 245–246 (atm.) d_4^{23} 1.0299; n_D^{23} 1.5744 oxime, m.p. 75.5–77 phenylhydrazone, m.p. 81–82 2,4-dinitrophenylhydrazone, m.p. 147 semicarbazone, m.p. 176–177	135
2-*n*-Pentyl-	b.p. 135–136 (11 mm.), 275–276 (atm.) d_4^{14} 0.9761; n_D^{14} 1.534 oxime, an oil phenylhydrazone, m.p. 80–81.5 (unstable) semicarbazone, m.p. 134	135; see also 137
2-Hexyl-	b.p. 146 (10 mm.) d_4^{15} 0.9857; n_D^{15} 1.5431	138
2-Alkoxyalkyl-3-(2-furyl)acroleins		
2-Methoxymethyl-	b.p. 129 (12 mm.) phenylhydrazone, m.p. 107 semicarbazone, m.p. 194	134
2-Ethoxymethyl-	b.p. 136 (12 mm.) phenylhydrazone, m.p. 144 semicarbazone, m.p. 172	134
2-*n*-Propoxymethyl-	b.p. 139 (10 mm.) aldazine, m.p. 119 phenylhydrazone, m.p. 146 semicarbazone, m.p. 168	134
2-*n*-Butoxymethyl-	b.p. 152 (12 mm.) phenylhydrazone, m.p. 102	134
2-(1-Hydroxyethyl)-	b.p. 154 (10 mm.) phenylhydrazone, m.p. 136 semicarbazone, m.p. 211	134
2-(2-Hydroxyethyl)-	b.p. 178 (10 mm.) phenylhydrazone, m.p. 110	134
2-(1-Methoxyethyl)-	b.p. 121 (10 mm.) phenylhydrazone, m.p. 158 semicarbazone, m.p. 208	134
2-Tetrahydrofurfuryloxymethyl-	b.p. 199 (16 mm.) phenylhydrazone, m.p. 126	134

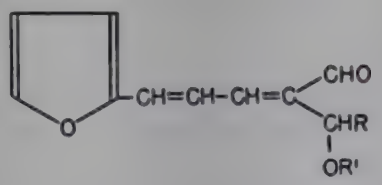
TABLE 2. POLYENIC ALDEHYDES WITH TERMINAL FURYL GROUP

Vinylogs of 3-(2-furyl)acrolein



Compounds	*n*	Physical constants (°C.) and derivatives	Ref.
5-(2-Furyl)-2,4-pentadienal	2	m.p. 66; b.p. 130–160 (15 mm.) oxime, m.p. 127 aldazine, m.p. 206 phenylhydrazone, m.p. 153	132, 139, 133; see also 140, 140a
7-Furyl-2,4,6-heptatrienal	3	m.p. 111 phenylhydrazone, m.p. 183	132, 131
9-Furyl-2,4,6,8-nonatetraenal	4	m.p. 155	131
11-Furyl-2,4,6,8,10-undecapentaenal	5	m.p. 194	131
13-Furyl-2,4,6,8,10,12-tridecahexaenal	6	m.p. 218	131
15-Furyl-2,4,6,8,10,12,14-pentadecaheptaenal	7	m.p. 230 (dec.)	131

Substituted vinylogs of 3-(2-furyl)acrolein



	R	R′		
2-(Methoxymethyl)-5-(2-furyl)pentadienal	H	CH_3	b.p. 168 (12 mm.) phenylhydrazone, m.p. 126 semicarbazone, m.p. 192	134
2-(1-Methoxyethyl)-5-(2-furyl)pentadienal	CH_3	CH_3	b.p. 162 (13 mm.) semicarbazone, m.p. 256	134

[141] Schmidt, *Ber.*, **13**, 2342 (1880).

[142] Röhmer, *Ber.*, **31**, 281 (1898).

[143] König and Hey, German Pat. 330,358 (1919); *C. A.*, **15**, 2102 (1921).

[144] Takamoto and Hirohashi, *J. Pharm. Soc. Japan*, **48**, 446, (1928); *C. A.*, **22**, 3409 (1928).

[145] Likhosherstov, Arsenyuk, Zeberg and Karitskaya, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20**, 627 (1950); *C. A.*, **44**, 7823 (1950).

For the condensation with creatinine, see Cornthwaite and Jordan.[149] The catalytic hydrogenation of furylacrolein is discussed elsewhere (Chapter 15). Reduction with aluminum ethoxide gives rise to 3-(2-furyl)allyl alcohol.[145]

Oxidation in aqueous calcium hydroxide by air or oxygen in the presence of colloidal silver produces 3-(2-furyl)acrylic acid[150] (see also [151]).

Potassium bisulfite adds to the olefinic bond to give potassium 1-furyl-2-formylethanesulfonate, $C_4H_3O—CH(SO_3K)—CH_2CHO$.[152]

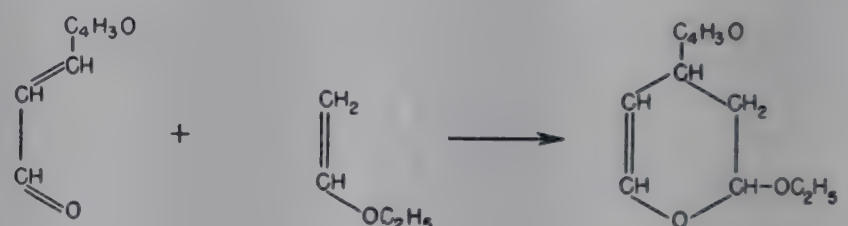
Dialkyl phosphites also add to furylacrolein, under the influence of sodium alkoxide, but do so to the aldehyde group rather than to the lateral double bond. Thus, Pudovik[153] obtained the α-hydroxyphosphonic ester, VI (m.p. 106–107°) by reaction

$$C_4H_3O—CH{=}CH—CHO + (EtO)_2POH \xrightarrow{RONa} C_4H_3O—CH{=}CH—CHOH—PO(OEt)_2$$

VI

with diethyl phosphite. This is in contrast to the behavior of furfurylideneacetone which gives rise to the appropriate β-ketophosphonic ester, addition taking place at the double bond adjacent to the carbonyl group.

Vinyl ethers add to the 1,4-conjugated system made up by the olefinic double bond and the aldehyde group. Thus, heating furylacrolein with ethyl vinyl ether gives rise to 2-ethoxy-4-(2-furyl)-3,4-dihydro-1,2-pyran, VII, b.p. 98° (5 mm.); d_4^{25} 1.083; n_D^{25} 1.4885.[154]



VII

2-Chloro-3-(2-furyl)acrolein: $C_4H_3O—CH{=}CCl—CHO$; m.p. 79°. **Oxime,** sublimes at 110°; **phenylhydrazone,** m.p. 157°. Obtained in 8–9 per cent yield by condensation of furfural with chloroacetaldehyde under carefully controlled conditions of alkalinity. Oxidation with silver oxide produced the corresponding acid, m.p. 142°; the Perkin reaction with sodium acetate and acetic anhydride gave rise to 5-(2-furyl)-4-chloro-2,4-pentadienoic acid, m.p. *ca.* 168°.[155]

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[146] König, *J. prakt. Chem.*, **88,** 193 (1913).

[147] Levine and Seaman, *Biochem. J.*, **27,** 2047 (1933).

[148] Rudchenko, *J. Gen. Chem. U.S.S.R.*, **10,** 1953 (1940); *C. A.*, **35,** 4011 (1941).

[149] Cornthwaite and Jordan, *J. Am. Chem. Soc.*, **56,** 2733 (1934).

[150] Gavatin (to Mo Och Domsjö Aktiebolat), Swedish Pat. 118,461 (1947); *C. A.*, **42,** 223 (1948).

[151] Dinelli, *Ann. chim. applicata*, **29,** 448 (1939); *C. A.*, **34,** 1903 (1940).

[152] Thurston (to American Cyanamid Company), U. S. Pat. 2,372,233 (1945); *C. A.*, **39,** 5023 (1945); British Pat. 592,747 (1947); *C. A.*, **42,** 2283 (1948); U. S. Pat. 2,385,314 (1945); *C. A.*, **40,** 609 (1946).

[153] Pudovik, *Doklady Akad. Nauk. S.S.S.R.*, **73,** 499 (1950); *C. A.*, **45,** 2856 (1951).

[154] Longley and Emerson, *J. Am. Chem. Soc.*, **72,** 3079 (1950).

[155] Mehne, *Ber.*, **21,** 423 (1888).

Chapter 11

KETONES

With a few important exceptions, all furan compounds possessing a ketonic function are dealt with in this chapter. These exceptions are the keto acids (see Chapters 12, 13), and those ketones wherein the furan nucleus is also substituted by nitro (see Chapter 4), or halogen (see Chapter 3).

2-Furyl Ketones

In this section we are concerned with those ketones in which a carbonyl group is directly attached to the furan nucleus at an α-carbon atom. For convenience, however, furoin, furil and related types which lie within the scope of this classification are considered later under the appropriate subheading.

General Methods of Preparation

Standard procedures have been employed for the preparation of alkyl and aryl 2-furyl ketones. They are obtained by:

(1) The Friedel-Crafts Reaction:

(*a*) *Acylation of Furan.* Formation of 2-furyl ketones may be accomplished successfully by Friedel-Crafts acylation of furan and its homologs, as indicated by the data listed in Table 1. The reaction itself has been discussed in some detail elsewhere (p. 66), and no additional comment is required.

(*b*) *Furoylation of Aromatic Types.* 2-Furoyl chloride condenses readily with benzene to give 2-furyl phenyl ketone in excellent yield. With thiophene, furoylation occurs even more easily so that, for example, the reaction has been conducted in benzene solution using stannic chloride with formation of 2-furyl 2-thienyl ketone.

$$C_4H_3O{-}COCl + C_6H_6 \xrightarrow{(AlCl_3)} C_4H_3O{-}CO{-}C_6H_5$$

$$C_4H_3O{-}COCl + C_4H_4S \xrightarrow[\text{in } C_6H_6]{(SnCl_4)} C_4H_3O{-}CO{-}C_4H_3S$$

Toluene, alkoxy- and halobenzenes likewise react with 2-furoyl chloride under the influence of aluminum chloride giving rise to the corresponding *p*-substituted phenyl furyl ketones. The orientation in these instances is

TABLE 1. ACYLATION OF FURAN AND ITS HOMOLOGS

Reactants (moles)		Catalyst (moles)	Conditions			Yield of ketone (%)	Ref.
			Solvent	Time	Temp. (°C.)		
Furan (1.0)	Ac_2O (1.0)	$SnCl_4$ (1.0)	C_6H_6	12–18 hrs.	25	64	1
Furan (0.5)	Ac_2O (1.0)	$ZnCl_2$ (0.015)	—	4 hrs.	0–20	66	2
Furan (0.5)	Ac_2O (1.0)	$ZnCl_2$ (0.015)	—	4 hrs.	30–60	40	2
Furan (0.5)	Ac_2O (1.0)	o-H_3PO_4 (0.04)	—	1 hr.	40–60	62	3, 4
Furan (1.0)	Ac_2O (2.0)	*o*-H_3PO_4 (0.08)	—	1.5–2 hrs.	45–60	to 77	5
Furan (1.0)	Ac_2O (1.0)	I_2 (4×10^{-4})	—	—	—	60	6, 7
Furan (1.0)	Ac_2O (1.0)	HI (1×10^{-2})	—	—	—	76	6, 7
Furan (0.5)	Ac_2O (1.0)	clay	—	3 hrs.	39–44	24	8, 9
Furan (0.5)	Ac_2O (1.0)	*p*-$CH_3C_6H_4SO_3H$ (0.01)	—	25 hrs.	56–64	45	4
Furan (2.0)	Ac_2O (1.0)	H_2SO_4 (0.02)	—	70 min.	10–20	42	4
Furan (1.0)	Ac_2O (1.15)	BF_3-Et_2O (14 g.)	—	see text		77	10
Furan (1.0)	Ac_2O (1.15)	BF_3-AcOH (18.5 g.)	—	see text		70*	11
Furan (3.0)	Ac_2O (1.0)	BF_3-MeOH (0.03)	—	2 hrs.	25	48	12, 13
Furan (1.2)	AcOH (1.0)	P_2O_5 (1.0)	C_6H_6	5 hrs.	room	7	14, 15
Furan (0.07)	AcCl (0.07)	$SnCl_4$ (0.07)	C_6H_6	2 hrs.	0–25	15	16
Furan (—)	AcCl (—)	$SnCl_4$ (—)	C_6H_6	—	—	44	1
Furan (—)	$ClCH_2COCl$ (—)	$AlCl_3$ (—)	—	—	—	21	17
Furan (0.2)	$BrCH_2COBr$ (0.2)	$AlCl_3$ (0.24)	CS_2	15 min.	25	38	18
Furan (1.0)	$(C_2H_5CO)_2O$ (1.0)	$SnCl_4$ (1.0)	C_6H_6	12–18 hrs.	25	51	1
Furan (—)	$(C_2H_5CO)_2O$ (—)	$ZnCl_2$ (—)	—	—	—	52	19
Furan (1.0)	$(C_2H_5CO)_2O$ (1.15)	BF_3-Et_2O (14 g.)	—	see text		81	10
Furan (1.0)	$(C_2H_5CO)_2O$ (1.15)	BF_3-AcOH (18.5 g.)	—	see text		67*	11
Furan (0.2)	C_2H_5COCl (0.2)	$AlCl_3$ (0.2)	CS_2	50 min.	0–25	36	20; see also 21, 22

Furan (1.0)	n-$(C_3H_7CO)_2O$ (1.0)	$SnCl_4$ (1.0)	C_6H_6	12–18 hrs.	25	70	1
Furan (1.0)	n-$(C_3H_7CO)_2O$ (1.15)	BF_3-Et_2O (14 g.)	—	see text		93	10
Furan (1.0)	n-$(C_3H_7CO)_2O$ (1.15)	BF_3-AcOH (18.5 g.)	—	see text		92*	11
Furan (0.2)	n-C_3H_7COCl (0.2)	$AlCl_3$ (0.2)	CS_2	50 min.	0–25	52	20
Furan (0.2)	i-C_3H_7COCl (0.2)	$AlCl_3$ (0.2)	CS_2	50 min.	0–25	45	20
Furan (0.2)	n-C_4H_9COCl (0.2)	$AlCl_3$ (0.2)	CS_2	50 min.	0–25	23	20
Furan (0.2)	n-$C_7H_{15}COCl$ (0.2)	$AlCl_3$ (0.2)	CS_2	50 min.	0–25	39	20
Furan (1.2)	$C_9H_{19}COOH$ (1.0)	P_2O_5 (1.0)	C_6H_6	4 hrs.	room	18	15
Furan (1.2)	$C_9H_{19}COOH$ (1.0)	P_2O_5 (0.5)	C_6H_6	4 hrs.	room	10	15
Furan (0.1)	$C_{11}H_{23}COCl$ (0.1)	$AlCl_3$ (0.1)	CS_2	—	reflux	—	23
Furan (0.1)	$C_{17}H_{35}COCl$ (0.1)	$AlCl_3$ (0.1)	CS_2	—	reflux	—	23
Furan (1.0)	Bz_2O (1.0)	$SnCl_4$ (1.0)	C_6H_6	12–18 hrs.	25	49	1
Furan (3.0)	Bz_2O (1.0)	H_2PO_2F-H_2O (0.03)	—	3 hrs.	40	70	3, 4
Furan (3.0)	Bz_2O (0.44)	BF_3-AcOH (0.025)	—	2 hrs.	32	87	13
Furan (1.2)	BzOH (1.0)	P_2O_5 (0.5)	C_6H_6	5 hrs.	room	78	14, 15
Furan (2.0)	BzCl (1.0)	I_2 (4×10^{-3})	—	5 hrs.	40–50	12	7
2-Methylfuran (0.06)	AcCl (0.21)	$AlCl_3$ (0.11)	CS_2	—	—	12	16; see also 21
2-Methylfuran (0.07)	AcCl (0.08)	$SnCl_4$ (0.07)	C_6H_6	15 min.	—	22	16
2-Methylfuran (0.04)	AcCl (0.1)	$ZnCl_2$ (0.06)	Et_2O	1 hr.	—	34	16
2-Methylfuran (0.50)	Ac_2O (0.58)	BF_3-Et_2O (7 g.)	—	30 min.	90–115	42	24

TABLE 1.—*Continued*

Reactants (moles)		Catalyst (moles)	Conditions			Yield of ketone (%)	Ref.
			Solvent	Time	Temp. (°C.)		
2-Methylfuran (0.50)	$(C_2H_5CO)_2O$ (0.58)	BF_3-Et_2O (7 g.)	—	30 min.	90–115	52	24
2-Methylfuran (0.50)	$(C_3H_7CO)_2O$ (0.58)	BF_3-Et_2O (7 g.)	—	30 min.	90–115	62	24
2-Methylfuran (0.1)	$C_{17}H_{35}COCl$ (0.1)	$AlCl_3$ (0.1)	CS_2	—	reflux	—	23
2,5-Dimethylfuran (1.0)	Ac_2O (1.3)	$SnCl_4$ (0.004)	—	4 hrs.	reflux	77	25
2,5-Dimethylfuran (0.14)	Ac_2O (—)	$FeCl_3$ (—)	—	—	—	42	20
2,5-Dimethylfuran (1.0)	Ac_2O (1.15)	BF_3-Et_2O (14 g.)	—	—	see text	65	11
2,5-Dimethylfuran (1.0)	$(C_2H_5CO)_2O$ (1.15)	BF_3-Et_2O (14 g.)	—	—	see text	63	11
2,5-Dimethylfuran (1.0)	n-$(C_3H_7CO)_2O$ (1.15)	BF_3-Et_2O (14 g.)	—	—	see text	60	11
2,5-Dimethylfuran (—)	Bz_2O (—)	$FeCl_3$ (—)	CS_2	—	—	7	20
2,5-Dimethylfuran (—)	Bz_2O (—)	$SnCl_4$ (—)	C_6H_6	—	—	29	20
2,5-Dimethylfuran (—)	BzCl (—)	$AlCl_3$ (—)	CS_2	—	—	7	20
2,5-Diphenylfuran (0.25)	Ac_2O (0.28)	$SnCl_4$ (0.25)	C_6H_6	1 hr.	15–20	80	26
2,5-Diphenylfuran (0.25)	$(C_2H_5CO)_2O$ (0.28)	$SnCl_4$ (0.25)	C_6H_6	1 hr.	15–20	72	26

* Yield values taken from Heid and Levine.[10a]

established by oxidation to the appropriate *p*-substituted benzoic acids.[27]

$$C_4H_3O{-}COCl \xrightarrow[C_6H_5X]{(AlCl_3)} C_4H_3O{-}CO{-}C_6H_4X{-}p \xrightarrow{(O)} X{-}C_6H_4(COOH){-}p$$

Reaction of 2-furoyl chloride, phenol and aluminum chloride yields *p*-2-furoylphenol along with a considerable quantity of phenyl 2-furoate. That this reaction may involve a Fries rearrangement of the ester to the ketone is indicated by isolation of the latter on treatment of phenyl 2-furoate with aluminum chloride. The structure of the ketone was established by methylation and subsequent oxidation to the known *p*-anisic acid.[28] Furoylation of resorcinol under similar conditions gave a good yield of a ketone, believed to be 4-(2-furoyl)resorcinol. On the other hand, when the reaction was carried out with hydroquinone the only product appeared to be the half ester, *p*-hydroxyphenyl 2-furoate.[28]

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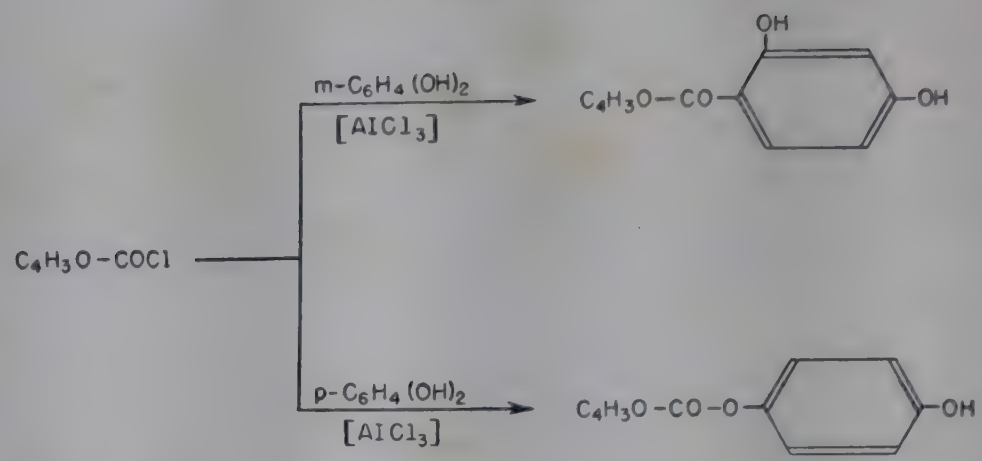
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TABLE 2. FURANCARBONYL CHLORIDES IN THE FRIEDEL-CRAFTS REACTION

Reactants (moles)		Catalyst (moles)	Solvent	Product	Yield (%)	Ref.
2-Furoyl chloride (0.075)	furan (0.075)	$SnCl_4$ (0.075)	C_6H_6	di-2-furyl ketone	4	16
2-Furoyl chloride (0.075)	furan (0.075)	$AlCl_3$ (0.15)	CS_2	di-2-furyl ketone	1	16
2-Furoyl chloride (0.2)	thiophene (0.2)	$SnCl_4$ (0.2)	C_6H_6	2-furyl 2-thienyl ketone	66	29
2-Furoyl chloride (—)	2,5-dimethylthiophene (—)	$AlCl_3$ (—)	CS_2	2-furyl 2,5-dimethyl-3-thienyl ketone	—	30
2-Furoyl chloride (0.16)	benzene (xs)	$AlCl_3$ (0.21)	C_6H_6	2-furyl phenyl ketone	85	31, 27
2-Furoyl chloride (0.66)	toluene (xs)	$AlCl_3$ (0.73)	$C_6H_5CH_3$	2-furyl *p*-tolyl ketone	80	32; see also 33, 34
2-Furoyl chloride (0.17)	chlorobenzene (0.18)	$AlCl_3$ (0.15)	CS_2	2-furyl *p*-chlorophenyl ketone	95	33
2-Furoyl chloride (—)	bromobenzene (—)	$AlCl_3$ (—)	CS_2	2-furyl *p*-bromophenyl ketone	49	27; see also 33
2-Furoyl chloride (0.25)	phenol (0.2)	$AlCl_3$ (0.21)	CS_2	phenyl 2-furoate + *p*-2-furoylphenyl 2-furoate	32 —	28
2-Furoyl chloride (0.2)	phenol (0.22)	$AlCl_3$ (0.1)	CS_2	phenyl 2-furoate	58	28
2-Furoyl chloride (0.2)	phenol (0.2)	$AlCl_3$ (0.1)	$C_6H_5NO_2$	*p*-2-furoylphenol + phenyl 2-furoate	25 58	28
2-Furoyl chloride (0.5)	resorcinol (0.5)	$AlCl_3$ (0.25)	CS_2 or $C_6H_5NO_2$	4-(2-furoyl)resorcinol	80	28
2-Furoyl chloride (0.2)	hydroquinone (0.2)	$AlCl_3$ (0.1)	CS_2 or $C_6H_5NO_2$	*p*-hydroxyphenyl 2-furoate	82	28
2-Furoyl chloride (—)	catechol (—)	$AlCl_3$ (—)	—	greenish-blue product	—	28
2-Furoyl chloride (0.5)	anisole (0.5)	$AlCl_3$ (—)	CS_2	2-furyl *p*-methoxyphenyl ketone	60	32; see also 33

TABLE 2—*Continued*

Reactants (moles)		Catalyst (moles)	Solvent	Product	Yield (%)	Ref.
2-Furoyl chloride (—)	phenetole (—)	$AlCl_3$ (—)	CS_2	2-furyl *p*-ethoxyphenyl ketone	—	27
2-Furoyl chloride(0.1)	veratrol (0.1)	$AlCl_3$ (0.11)	CS_2	2-furyl 3,4-dimethoxyphenyl ketone	70	32
2-Furoyl chloride (0.06)	naphthalene (0.06)	$AlCl_3$ (0.07)	CS_2	2-furyl 1-naphthyl ketone	—	35
5-*t*-Butyl-2-furoyl chloride (0.1)	benzene (xs)	$AlCl_3$ (0.1)	C_6H_6	5-*t*-butyl-2-furyl phenyl ketone	70	20
3,4-Diphenyl-2-furoyl chloride (0.08)	benzene (xs)	$AlCl_3$ (0.15)	C_6H_6	3,4-diphenyl-2-furyl phenyl ketone	—	36
5-Nitro-2-furoyl chloride (—)	benzene (xs)	$AlCl_3$ (—)	C_6H_6	5-nitro-2-furyl phenyl ketone	63	37
2,5-Furandicarbonyl chloride (—)	benzene (xs)	$AlCl_3$ (—)	C_6H_6	2,5-dibenzoylfuran	96	38



(2) Action of the Grignard reagent on:

(*a*) *2-Furonitrile.*[39, 40, 41, 42, 43]

$$C_4H_3O{-}CN \xrightarrow{RMgX} C_4H_3O{-}CR{=}NMgX \xrightarrow{HCl} C_4H_3O{-}COR$$

The reverse reaction of furylmagnesium iodide with an aliphatic nitrile was employed by Ralston and Christensen.[23]

(*b*) *N,N-disubstituted 2-furamides.*[44, 45]

(*c*) *2-Furoyl chloride.*[29] Use of dialkylcadmium in place of the Grignard is described by Gilman and Nelson[46] (see also [47]).

(*d*) *2-Furoic acid*[48] *and ester*[29] (see also p. 518).

(3) Splitting the appropriate β-ketocarboxylic esters (2-furoylacetic ester and its homologs) with aqueous mineral acids[49, 50, 51, 52, 29, 53] (see also p. 605).

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[34] Straley, *Iowa State Coll. J. Sci.*, **11**, 115 (1936).
[35] Scholl and Seer, *Ann.*, **394**, 111 (1912).
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[51] Ciusa, *Gazz. chim. ital.*, **52**, II, 43 (1922); *C. A.*, **17**, 1478 (1923).
[52] Rinkes, *Rec. trav. chim.*, **51**, 349 (1932).
[53] Mironescu and Ioanid, *Bul. soc. chim. Romania*, **17**, 107 (1935); *C. A.*, **30**, 1053 (1936).

$$C_4H_3O—COCRR'COOC_2H_5 \xrightarrow{HCl} C_4H_3O—COCHRR' + CO_2 + C_2H_5OH$$

(4) Decarboxylation of 5-acyl-2-furoic acids.[20]

(5) Treatment of 2-furylmercuric chloride with an alkyl halide.[20]

(6) Action of diazoalkanes on the appropriate furancarbonal.[54]

2-Furyl Methyl Ketone and Its Homologs

2-Furyl methyl ketone (α-furylethanone) is a colorless liquid which discolors slowly on standing in air. It occurs as one component of the lighter fraction of wood tar[55, 56] (see also [56]), and as an end product in animal metabolism as a result of feeding β-2-furylacrylic acid.[57] It is obtained by the general procedures 1a, 2a, 3 and 4 which have been described, and in low yield by dehydrogenation of furylmethyl carbinol over aluminum.[58] Preparation by the action of ketene on 2-furylmercuric chloride was studied by Wright[59] who found chloroform to be the preferred reaction medium. Webb[60] obtained furyl methyl ketone by passing methyl furoate and acetic acid over thorium dioxide at elevated temperature.

Related Ketones.

5-Methyl-2-furyl methyl ketone: (5-methyl-2-acetylfuran); b.p. 74° (12 mm.); **oxime,** m.p. 78–79°; **tosylated oxime,** m.p. 111° (dec.); **semicarbazone,** m.p. 190–191°[16, 24, 62] (see also [21]). For cyanoethylation, see Acara and Levine.[64] For reaction with isatin to form 2-(5-methyl-2-furyl)cinchoninic acid (m.p. 237°), see Casoni.[64a]

5-Methyl-2-furyl ethyl ketone: (5-methyl-2-propionylfuran); b.p. 69.5–70° (4.5 mm.), 94–96° (14 mm.); **oxime,** m.p. 110°; **semicarbazone,** m.p. 156–157°, 162–164°; from 5-methylfurfural and diazoethane[54]; by acylation of methylfuran with propionic anhydride in the presence of boron fluoride etherate.[24]

5-Methyl-2-furyl propyl ketone: (5-methyl-2-butyrylfuran); b.p. 80–81° (4 mm.); **semicarbazone,** m.p. 149–150°.[24]

5-Methyl-2-furyl heptadecyl ketone: (5-methyl-2-stearylfuran): m.p. 68–69°.[23]

5-Hydroxymethyl-2-furyl methyl ketone: (5-acetofurfuryl alcohol); b.p. 130° (3 mm.); m.p. 43–44°; **semicarbazone,** m.p. 194°. Prepared (a) by saponification of the corresponding acetate (m.p. 46.5–47°; semicarbazone, m.p. 173–174°) derived from 5-chloromercurifurfuryl acetate and ketene,[59] and (b) by the action of diazomethane on 5-(hydroxymethyl)furfural.[54]

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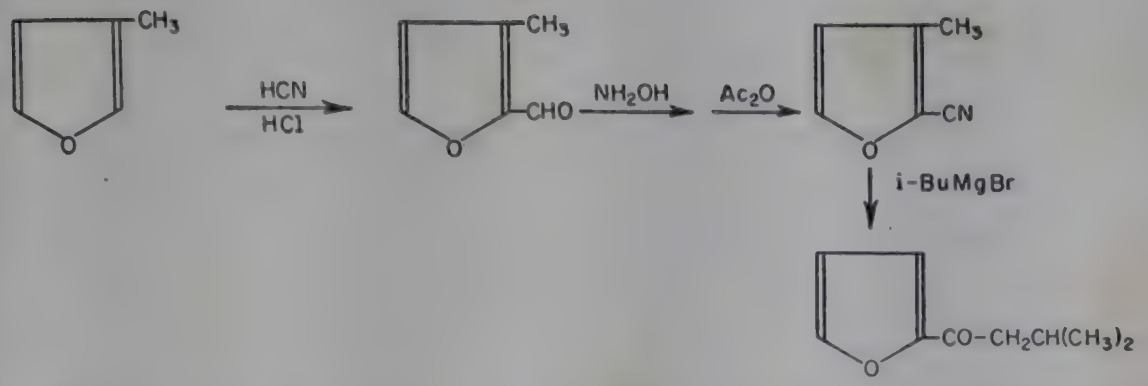
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[60] Webb and Webb, *J. Am. Chem. Soc.*, **71**, 2285 (1949).
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[63] Bruson and Riener, *J. Am. Chem. Soc.*, **70**, 214 (1948).
[64] Acara and Levine, *J. Am. Chem. Soc.*, **72**, 2864 (1950).
[64a] Casoni, *Boll. sci. facoltà chim. ind. Bologna*, **8**, 141 (1950); *C. A.*, **45**, 8014 (1951).

TABLE 3. ALKYL 2-FURYL KETONES

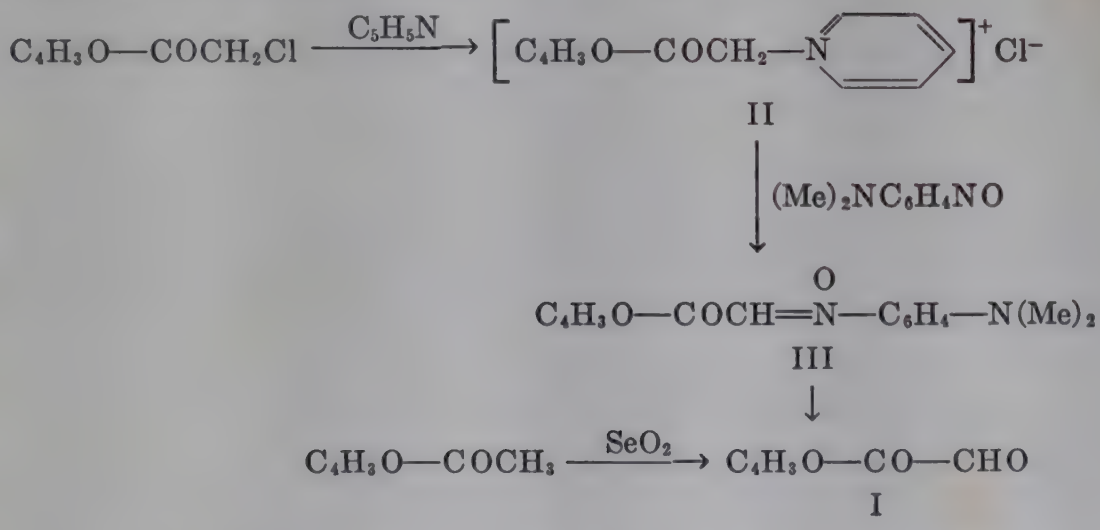
Alkyl radical	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
Methyl	m.p. 30–32, 33 b.p. 45–48 (5 mm.), 62–63 (12 mm.), 168–169 (760 mm.) d^{20} 1.0175; n_D^{20} 1.50167	oxime, 102–103.5, 104 oxime acetate, 96 oxime trichloroacetate, 98 oxime benzoate, 97–98 oxime tosylate, 80 (dec.) phenylhydrazone, 86.5 2,4-dinitrophenylhydrazone, 219–220, 223 semicarbazone, 149–150, 151–152	49, 50, 39, 40, 51, 16, 52, 20, 29, 1, 42, 59, 6, 2, 3, 14, 12, 8, 10, 5, 11, 61, 54, 62, 60
Ethyl	m.p. 27–28, 28–29 b.p. 61–63 (6 mm.), 182–183 (atm.) d^{28} 1.0626; n_D^{28} 1.49837	oxime, 77 oxime tosylate, 68 semicarbazone, 186–187, 188–190	39, 40, 44, 20, 22, 46, 53, 1, 42, 45, 10, 63, 11, 21, 19, 54, 62
n-Propyl	b.p. 76–78 (7 mm.), 96 (20 mm.) d^{20} 1.0485, d_{25}^{25} 1.041 n_D^{20} 1.49165, n_D^{25} 1.4922	semicarbazone, 189–190, 190–191	39, 40, 44, 20, 53, 1, 48, 10, 63, 11
i-Propyl	b.p. 86–87 (18 mm.) d_{25}^{25} 1.032; n_D^{25} 1.4888		20, 53
Cyclopropyl	b.p. 75 (23 mm.)	semicarbazone, 167	53
n-Butyl	b.p. 108–109 (18 mm.) d_{25}^{25} 1.012; n_D^{25} 1.4900	semicarbazone, 158–159	20
sec.-Butyl	b.p. 96 (16 mm.)	semicarbazone, 174	53
i-Butyl	b.p. 98 (18 mm.), 207 (760 mm.) d^{19} 1.0110; n_D^{19} 1.48905	semicarbazone, 174	39, 40, 45, 48
n-Pentyl	b.p. 116–119 (16 mm.) d_{25}^{25} 0.9954; n_D^{25} 1.4864	semicarbazone, 110–112	20
i-Pentyl	b.p. 119 (22 mm.), 221 (760 mm.) d^{22} 0.9900; n_D^{22} 1.48385	semicarbazone, 101	39, 40, 48
Diethylmethyl	b.p. 97 (17 mm.)	semicarbazone, 162	53
Nonyl	b.p. 150–154 (4 mm.)	2,4-dinitrophenylhydrazone, 90.5–91.5	14
Undecyl	b.p. 165–168 (5 mm.)		23
Heptadecyl	m.p. 56–57		23

3-Methyl-2-furyl *i*-butyl ketone: (Elsholtzione; Elsholtzia ketone); obtained from the essential oils of *Elsholtzia cristata Willdenow*.[39, 65] It is a pleasant smelling, almost colorless oil, b.p. 210° (764 mm.), 92° (9 mm.); d^{20} 0.9817; **oxime**, m.p. 54–54.5°; **semicarbazone**, m.p. 171°. Synthesis was accomplished from 3-methylfuran as shown.[66]

[65] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta Phytochim. Japan*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).



2-Furyl methyl ketone and its homologs are reported to give a relatively strong Liebermann color reaction.[39] Oxidation with sodium and pentyl nitrite[39, 40] or with sodium hypochlorite[67, 24] produces the furoic acid. Reduction to 2-alkylfurans has been accomplished by the Wolff-Kizhner procedure whereby the hydrazone is decomposed by potassium hydroxide.[68, 20, 21] With selenium dioxide, furyl methyl ketone is oxidized to furylglyoxal, I, a pungent yellow oil, b.p. 65–66° (4 mm.); mono-semicarbazone, m.p. 215° (dec.).[47] I, as the hydrate (m.p. 68–69°) is also obtainable from chloromethyl 2-furyl ketone by way of furoylmethylpyridinium chloride (II), m.p. 178–179° [the perchlorate salt, m.p. 146°, is also known[69]], and furoyl-N-(4′-dimethylaminophenyl)nitrone (III), m.p. 123–125°.[47]

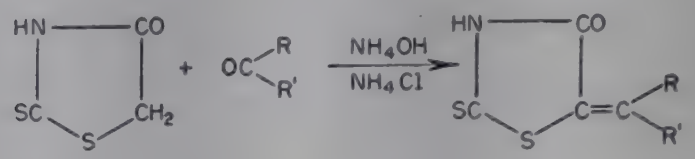


The Grignard reagent adds normally to furyl alkyl ketones to give, on subsequent hydrolysis, the expected tertiary alcohol.[70, 33] A report on the pharmacological properties of furyl methyl ketone and other mixed 2-furyl ketones indicates them to be more toxic than hypnotic in their action.[29] In connection with a study of the fungicidal properties of rhodanine deriva-

[66] Reichstein, Zschokke and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
[67] Farrar and Levine, *J. Am. Chem. Soc.*, **71**, 1496 (1949).
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[70] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15**, 1118 (1932).

tives, Brown *et al.*[71] carried out condensation reactions involving rhodanine and several alkyl furyl ketones.

TABLE 4. RHODANINE DERIVATIVES[71]



Ketone	Product		
	R	R′	m.p. (°C.)
2-Furyl methyl	C_4H_3O	CH_3	243.5–244.5
2-Furyl ethyl	C_4H_3O	C_2H_5	180.5–181
2-Furyl propyl	C_4H_3O	C_3H_7	159.5–160.5
2-(5-Methylfuryl) methyl	$CH_3—C_4H_2O$	CH_3	248 (dec.)
Furfurylideneacetone	$C_4H_3O—CH=CH$	CH_3	210–214 (dec.)

Sulfonation of furyl methyl ketone with pyridine-SO_3 complex gives rise to 5-acetyl-2-furansulfonic acid which was isolated as the barium salt in 82 per cent yield.[72]

The thioacetal, α-furylethanone diethylmercaptol [b.p. 93–96° (2.5 mm.)], has been prepared from the furyl methyl ketone and ethyl mercaptan in toluene using hydrogen chloride as the condensing agent.[73]

A number of typical condensation reactions involving the mobile α-hydrogen atoms have been carried out with the furyl alkyl ketones. With acrylonitrile in the presence of benzyltrimethylammonium hydroxide (Triton B), they undergo cyanoethylation as indicated below[63, 64] (see also [74]).

$$C_4H_3O—COCH_2R \xrightarrow[\text{(Triton B)}]{CH_2=CHCN} C_4H_3O—CO—CR(CH_2CH_2CN)_2$$

R	m.p. (°C)
CH_2CH_2CN	121–122
CH_3	49
C_2H_5	102

Ciusa[51] (see also [64a]) carried out the Pfitzinger reaction with furyl methyl ketone and isatin in aqueous potassium hydroxide, and reported the forma-

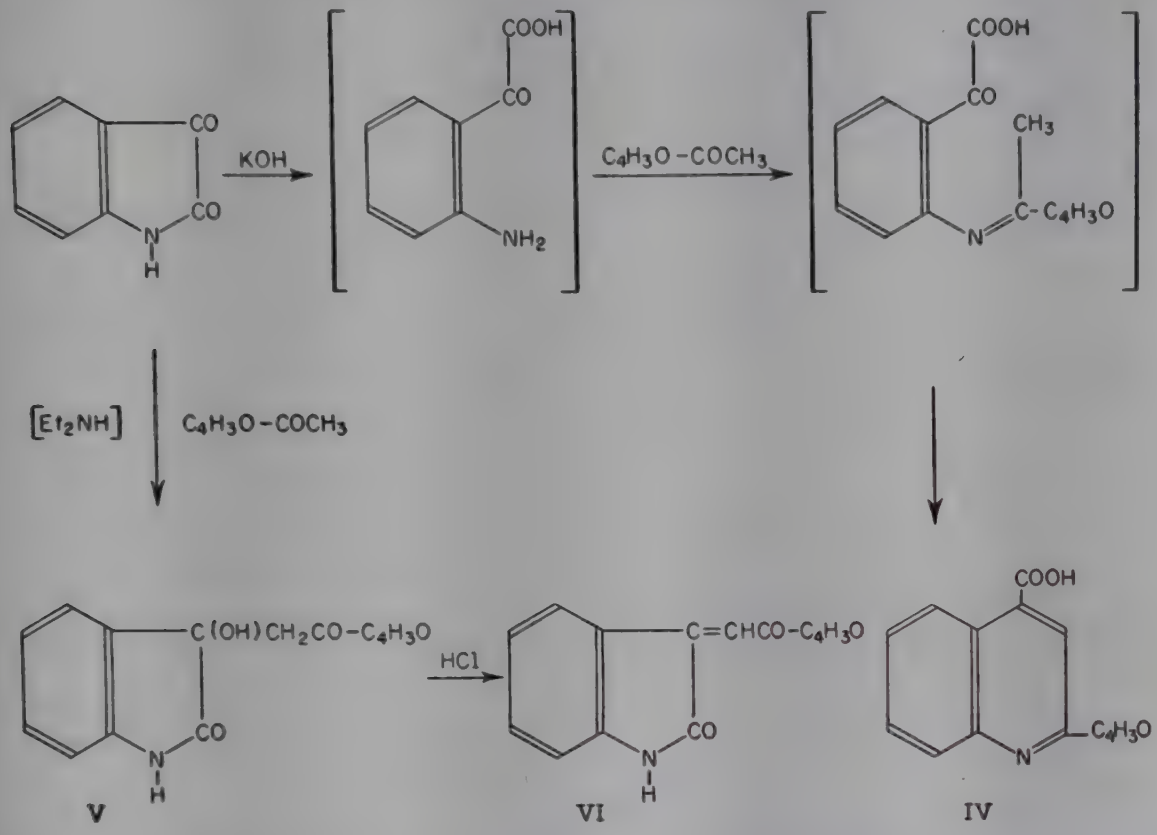
[71] Brown, Bradsher, McCallum and Potter, *J. Org. Chem.*, **15**, 174 (1950).

[72] Terent'ev, Kazitsyna and Turovskaya, *Vestnik Moskov. Univ.*, **3**, 159 (1948); *C. A.*, **44**, 5862 (1950).

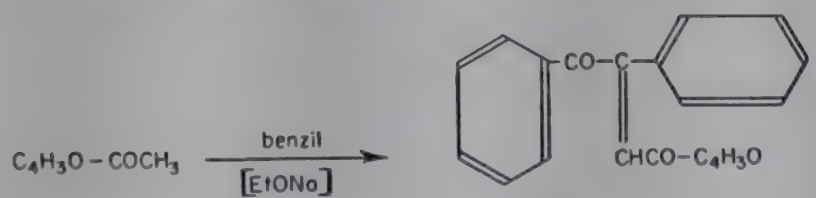
[73] Kipnis and Ornfelt, *J. Am. Chem. Soc.*, **71**, 2271 (1949).

[74] Zellars and Levine, *J. Org. Chem.*, **13**, 911 (1948).

tion of 2-furylcinchoninic acid, IV, although the observed melting point (m.p. 149°) is suspiciously low (see Table 5, p. 360). When the same reagents are condensed under the influence of diethylamine, there is produced 3-hydroxy-3-furacyloxindole (V) which, in the presence of hydrochloric acid, loses the elements of water to give 3-furacylideneoxindole, VI, m.p. 207–208°.[75] The reactions involved are illustrated below (see [76]). Under



the influence of sodium ethoxide the ketone condenses with benzil to form the diacylstyrene, VII, m.p. 168°.[77] An aliphatic hydrogen atom may also



VII

be replaced by an acyl group to form a 1,3-diketone, a reaction which is considered elsewhere (p. 439).

2-Furyl vinyl ketone is obtained by treating furyl methyl ketone with formaldehyde in the presence of potassium carbonate or other basic catalyst,

[75] Maxim and Petrascu, *Compt. rend. acad. sci. Roumanie*, **8**, 65 (1946–47); *C. A.*, **43**, 1411 (1949).

[76] Lindwall and MacLennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

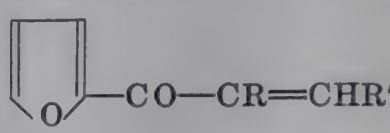
[77] Allen and Hubbard, *J. Am. Chem. Soc.*, **52**, 384 (1930).

and dehydrating the intermediate aldol.[78] Under the same conditions, furyl ethyl ketone gives rise to furyl isopropenyl ketone.[78] Linear polymers of these ketones are readily obtained using standard procedures.[78]

$$C_4H_3O{-}COCH_2R \xrightarrow{CH_2O} [C_4H_3O{-}COCHRCH_2OH] \xrightarrow{-HOH} C_4H_3O{-}COCR{=}CH_2$$

Related vinyl ketones have been obtained by condensing furyl methyl ketone with benzaldehyde, 2-thenaldehyde and furfural. In these instances, dehydration of the intermediate addition products occurs spontaneously, the unsaturated ketones being obtained directly in crystalline form and in high yield.

TABLE 5. VINYL 2-FURYL KETONES



Compound	Physical constants (°C.)	Ref.
Furyl vinyl ketone	b.p. 85 (10 mm.)	78
Furyl isopropenyl ketone	b.p. 92 (10 mm.)	78
Furyl styryl ketone (benzylideneacetylfuran)	m.p. 87–88, 88–89*	79, 42, 80
2-Furyl β-2-thienylvinyl ketone (thenylideneacetylfuran)	m.p. 81–82*	79
2-Furyl β-2-furylvinyl ketone (furfurylideneacetylfuran)	m.p. 88–89, 89–89.5*	79, 5, 81

* These products exhibit polymorphism (see [79]).

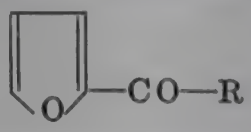
Catalytic hydrogenation of these vinyl ketones over palladium or nickel-kieselguhr saturates first the olefinic double bond. Thus, furyl furylvinyl ketone has been reduced predominantly to 1,3-difuryl-1-propanone by stopping the reaction after one mole of hydrogen has been absorbed.[5] Furyl styryl ketone behaves similarly.[42] The products along with the other reported aralkyl furyl ketones are tabulated in Table 6.

2-Furyl Hydroxymethyl Ketone and Related Products

When 2-furoyl chloride is added to a cold, ethereal solution of diazomethane, there is obtained the diazomethyl ketone, 2-furoyldiazomethane, I[85] (see also [86]). Interaction of I with dilute sulfuric acid gives rise to 2-furyl

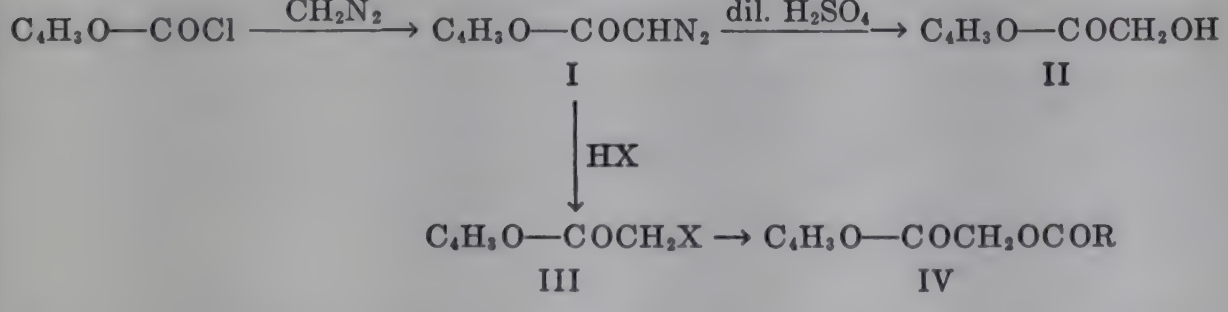
[78] Barnes (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,309,727 (1943); *C. A.*, **37**, 3767 (1943).
[79] Weygand and Strobelt, *Ber.*, **68**, 1839 (1935).
[80] Asahina and Mayeda, *J. Pharm. Soc. Japan*, **53**, 548 (1933); *C. A.*, **27**, 4229 (1933).
[81] Alexander, Hafner, Smith and Schniepp, *J. Am. Chem. Soc.*, **72**, 5506 (1950).
[82] Dakin, *Chem. Ztg.*, **19**, 1939 (1895).
[83] Kleucker, *Ber.*, **55**, 1634 (1922).
[84] MacNair, *Ann.*, **258**, 220 (1890).
[85] Burger and Harnest, *J. Am. Chem. Soc.*, **65**, 2832 (1943).
[86] Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).

TABLE 6. ARALKYL 2-FURYL KETONES



Compound	Physical constants and derivatives (°C.)	Ref.
Benzyl furyl ketone ($R=C_6H_5CH_2$)	m.p. 47, 47–48 b.p. 150–154 (15 mm.) oxime, m.p. 125–126 semicarbazone, m.p. 171–172 2,4-dinitrophenylhydrazone, m.p. 179	42; see also 82, 40
2-Furyl *p*-nitrobenzyl ketone ($R = p\text{-}NO_2C_6H_4CH_2$)	m.p. 158–159 oxime, m.p. 136–138	83
1-Furyl-3-phenylpropan-1-one ($R = C_6H_5CH_2CH_2$)	b.p. 185 (12 mm.) 2,4-dinitrophenylhydrazone, m.p. 165	42
Furfuryl furyl ketone (desoxyfuroin) ($R = 2\text{-}C_4H_3O\text{—}CH_2$)	m.p. 20 b.p. 159–160 (27 mm.), 250–260 (755 mm.) oxime, m.p. 94–95	84, 82
1,3-Difurylpropan-1-one ($R = 2\text{-}C_4H_3O\text{—}CH_2CH_2$)	b.p. 104–110 (0.5 mm.) n_D^{27} 1.5400; d_4^{27} 1.1642 oxime, m.p. 83–84 2,4-dinitrophenylhydrazone, m.p. 157.5–159.5	5

hydroxymethyl ketone, II[87]; with concentrated halogen acids there is formed the appropriate furyl halomethyl ketone, III,[85, 88, 89, 89a, 47] from which the esters, IV, may be synthesized.[90]



Hydroxymethyl 2-furyl ketone: II; m.p. 81–82°; **oxime,** m.p. 132–134°; **oxime tosylate,** m.p. 86–87° (dec.). Obtained in 74 per cent yield by the procedure illustrated above.[87, 62]

[87] Kipnis, Soloway and Ornfelt, *J. Am. Chem. Soc.*, **70**, 142 (1948).

[88] Burger (to Smith, Kline and French Laboratories), U. S. Pat. 2,400,913 (1946); *C. A.*, **40**, 5455 (1946).

[89] Knott, *J. Chem. Soc.*, **1947**, 1656.

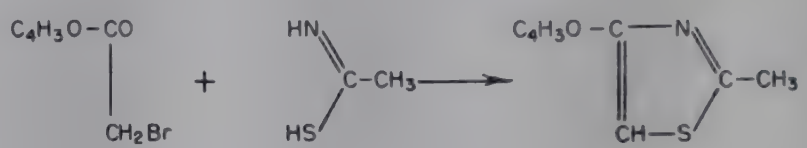
[89a] Kodak Ltd., Knott, Hamer and Rathbone, British Pat. 594,558 (1947); *C. A.*, **42**, 4079 (1948).

[90] Allcock, Kipnis, Ornfelt and Allen, *J. Am. Chem. Soc.*, **70**, 3949 (1948).

The 5-nitro derivative, m.p. 116–117.5°, is described by Stillman and Scott.[91] The following **esters**, IV, are known: R = CH_3, m.p. 31.5–32.5°, b.p. 70–75° (0.1 mm.), semicarbazone, m.p. 95–95.5°; R = n-C_3H_7, b.p. 110–112° (0.03 mm.), semicarbazone, m.p. 114–116°; R = 2-furyl, m.p. 95°, semicarbazone, m.p. 122–123° (dec.); R = C_6H_5, m.p. 75.5–76°, semicarbazone, m.p. 180–182° (dec.).[90, 87]

Chloromethyl 2-furyl ketone: III (X = Cl); m.p. 30.5°; b.p. 127–129° (27 mm.); d_{25}^{25} 1.340; n_D^{20} 1.5091; obtained in 88 per cent yield as indicated above[85, 88]; in 21 per cent yield by Friedel-Crafts reaction involving furan and chloroacetyl chloride in the presence of aluminum chloride.[22] It exerts a powerful lachrymatory action. Condensation with thiourea gives rise to 2-amino-4-(2-furyl)thiazole, m.p. 124.5°.[89] For the reactivity of the chlorine atom, see Catlin.[92]

Bromomethyl 2-furyl ketone: III (X = Br); m.p. 34°, 36–37°; b.p. 121–123 (20 mm.); d_4^{25} 1.5785; n_D^{25} 1.5783. Prepared as illustrated above[89]; also by bromination of furyl methyl ketone in carbon disulfide at room temperature and by condensation of bromoacetyl bromide with furan.[18] With thioacetamide it reacts to form 2-methyl-4-(2-furyl)thiazole, V [b.p. 128° (22 mm.); hydrobromide, m.p. 194–196°] which may be converted into 2-mercaptomethyl-4-(2-furyl)thiazole [b.p. 177° (22 mm.); hydrobromide, m.p. 208–210°].[89] With ethyl p-toluenesulfate, V gives rise to the quaternary ammonium salt from which one may obtain dyes related to the cyanine.[93, 94]



V

Dibromomethyl 2-furyl ketone: C_4H_3O—CO—$CHBr_2$; b.p. 145–147° (15 mm.); d_4^{25} 2.0040; n_D^{25} 1.6070. Obtained by treatment of 2-furyl methyl ketone in CS_2 with 2 molecular equivalents of bromine.[18]

Condensation of chloromethyl 2-furyl ketone with secondary amines results in the formation of the appropriate α-amino ketones, N-disubstituted aminomethyl 2-furyl ketones.[85, 88] Homologous aminoethyl ketones are also

$$C_4H_3O\text{—}COCH_2Cl \xrightarrow{R_2NH} C_4H_3O\text{—}COCH_2NR_2$$

known, synthesized from furyl methyl ketone by means of the Mannich reaction. Thus, reaction with formaldehyde and the hydrochloride salt of a secondary amine replaces a hydrogen atom of the methyl group by an aminomethyl radical.[95] Reduction to the corresponding amino alcohols is accomplished by means of aluminum isopropoxide[85, 88].

$$C_4H_3O\text{—}COCH_3 \xrightarrow[CH_2O]{R_2NH\cdot HCl} C_4H_3O\text{—}COCH_2CH_2NR_2\cdot HCl$$

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[91] Stillman and Scott (to Eaton Laboratories, Inc.), U. S. Patent 2,416,235 (1947); *C. A.*, **41**, 3489 (1947).

[92] Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935).

[93] Middleton (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,524,674 (1950).

[94] E. I. du Pont de Nemours and Co., British Pat. 571,077 (1945).

[95] Levy and Nisbet, *J. Chem. Soc.*, **1938**, 1053.

TABLE 7. AMINOALKYL 2-FURYL KETONES

Aminoalkyl group	Physical constants and derivatives (°C.)	Ref.
Diethylaminomethyl	b.p. 100–104 (4 mm.)	88
Piperidinomethyl	b.p. 139–140 (4 mm.) hydrochloride, m.p. 264–266 (dec.)	85, 88
(4-Methylpiperidino)methyl	b.p. 133–139 (4 mm.) hydrochloride, m.p. 253–265	85, 88
Morpholinomethyl	hydrochloride, m.p. 221–229	85, 88
2-Dimethylaminoethyl	hydrochloride, m.p. 178	95; see also 96
2-Dipropylaminoethyl	hydrochloride, m.p. 129–130 (dec.) cyanohydrin, m.p. 45	95, 96
2-Dibutylaminoethyl	hydrochloride, m.p. 111	95
2-Bis(β-hydroxyethyl)aminoethyl	hydrochloride, m.p. 100–101	95
2-Piperidinoethyl	hydrochloride, m.p. 185–186	95

Aryl 2-Furyl Ketones

Phenyl 2-furyl ketone (furophenone) and related types have been prepared, for the most part, by the general methods 1b, 2a, and 2b described earlier. They are stable crystalline products which exhibit the normal ketone reactions and nuclear behavior. Thus, the usual carbonyl derivatives are formed by standard procedures. Sodium in alcohol reduces the carbonyl group to methylene.[97, 98] Condensation with succinic ester produces the appropriately substituted itaconic esters (see p. 634), although Buu-Hoi[99] reports failure in his attempt to effect a related condensation, that of phenyl 2-furyl ketone with phenylacetonitrile in the presence of sodium amide.

On sulfonation,[34] nitration,[37, 34] bromination[34] and alkylation[20] of phenyl furyl ketone, the first incoming group orients to the 5-position of the furan nucleus.

When treated with primary aromatic amines and their hydrochloride salts, the aryl furyl ketones are converted to 1,2-diaryl-3-hydroxypyridinium chlorides[42] (see also Chapter 14).

Miscellaneous

5-*t*-Butyl-2-furyl phenyl ketone: 2,5-$C_4H_2O(COC_6H_5)(t\text{-}C_4H_9)$; b.p. 180–182° (20 mm.); d_{25}^{25} 1.065; n_D^{25} 1.5665; in 30 per cent yield by alkylation of phenyl 2-furyl ketone with *t*-butyl chloride, and in 70 per cent yield by acylation of benzene with 5-*t*-butyl-2-furoyl chloride.[20]

[96] Knott, *J. Chem. Soc.*, **1947**, 1190.
[97] Kariyone, *J. Pharm. Soc. Japan*, **428**, 891 (1917); *C. A.*, **12**, 274 (1918).
[98] Reichstein, Grüssner and Zschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).

TABLE 8. ARYL 2-FURYL KETONES

Aryl radical	Physical constants (°C.)	Derivatives, m.p. (°C.)	Ref.
Phenyl	m.p. 43.5–44, 47 b.p. 142–145 (2 mm.), 285 (759 mm.) d^{20} 1.1732; n_D^{20} 1.57975	oxime, 132–133, 138–139 oxime tosylate, 188 (dec.) semicarbazone, 182, 210–211 2,4-dinitrophenylhydrazone, 179	31, 39, 27, 100, 29, 41, 42, 1, 45, 3, 14, 62, 4, 15; see also 43
o-Tolyl	b.p. 177 (22 mm.)	—	45
p-Tolyl	m.p. 41–42 b.p. 185.7 (18 mm.)	semicarbazone, 66	33, 34, 32
p-Hydroxyphenyl	m.p. 163–164, 164–165	—	28, 101
p-Methoxyphenyl	m.p. 60, 63, 64	oxime, 135–137 oxime tosylate, 119–120	28, 33, 32, 62
p-Ethoxyphenyl	m.p. 70, 73 b.p. 220 (25 mm.)	oxime, 145	27, 28, 101
p-Chlorophenyl	m.p. 42 b.p. 182 (14 mm.)	semicarbazone, 74	33
p-Bromophenyl	m.p. 51 b.p. 175–177 (7 mm.), 197 (14 mm.)	oxime, 122 semicarbazone, 84	27, 33
2,4-Dihydroxyphenyl	m.p. 123–124, 128	2,4-dinitrophenylhydrazone, 257	28, 42
2-Chloro-4-hydroxyphenyl	m.p. 181–182	—	101
2-Chloro-4-ethoxyphenyl	m.p. 115	—	101
2-Nitro-4-chlorophenyl	m.p. 93–94	—	102
3,4-Dimethoxyphenyl	m.p. 114	—	32
2,3,4-Trihydroxyphenyl*	m.p. 160	—	103
p-Biphenyl	m.p. 76 b.p. 250–252 (13 mm.)	—	99
2-Methyl-4-hydroxy-6-*i*-propylphenyl	m.p. 158	—	101
2-Methyl-4-methoxy-6-*i*-propylphenyl	b.p. 212–215 (17 mm.)	—	101
1-Naphthyl	—	—	35
2-Fluorenyl	m.p. 105 b.p. 264–265 (15 mm.)	—	104
9-Oxo-2-fluorenyl	m.p. 160–161	—	104
2-Dibenzofuryl	m.p. 84 b.p. 262–264 (15 mm.)	—	104
2-Quinolyl	m.p. 104	2,4-dinitrophenylhydrazone, 222–223	105

* Furan analog of Alizarin Yellow A prepared directly from pyrogallol and furoic acid.[108]

3,5-Diphenyl-2-furyl phenyl ketone: 2,3,5-$C_4HO(COC_6H_5)(C_6H_5)_2$; m.p. 118°; **oxime,** m.p. 152°; obtained by hydrolysis of 3-phenyl-2-dibenzoylcyclopropyl acetate and subsequent ring closure on boiling with hydrochloric acid.[106]

3,4-Diphenyl-2-furyl phenyl ketone: 2,3,4-$C_4HO(COC_6H_5)(C_6H_5)_2$; m.p. 128°; by condensation of 3,4-diphenyl-2-furoyl chloride with benzene under the influence of $AlCl_3$.[36]

[99] Buu-Hoi, Nguyen-Hoan, Lecocq and de Clercq, *Rec. trav. chim.*, **67**, 795 (1948).
[100] Gilman, Heckert, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **7**, 419 (1933).
[101] Buu-Hoi, *Rec. trav. chim.*, **68**, 759 (1949).
[102] Morton and Bannerman, *J. Am. Chem. Soc.*, **67**, 1503 (1945).
[103] Renshaw and Naylor, *J. Am. Chem. Soc.*, **44**, 862 (1922).
[104] Buu-Hoi and Royer, *Rec. trav. chim.*, **67**, 175 (1948).
[105] Brown, *J. Chem. Soc.*, **1949**, 2577.
[106] Kohler and Jones, *J. Am. Chem. Soc.*, **41**, 1249 (1919).

3,4,5-Triphenyl-2-furyl phenyl ketone: $2,3,4,5\text{-}C_4O(COC_6H_5)(C_6H_5)_3$; m.p. 166°; **oxime,** m.p. 230°; derived from tetraphenylcyclopentadienone[107] (see also [108, 109]).

Di-2-furyl Ketone and Related Products

Di-2-furyl ketone: m.p. 31–32, 33–34°; b.p. 110° (0.5 mm.); **semicarbazone,** m.p. 144–144.5°. Freundler[110] intimates that this ketone is present in small amount in the liquid product mixture obtained by dry distillation of barium furoate. Reichstein[16] was unable to isolate any by this procedure, but did succeed, in low yield, by (1) reaction of furoyl chloride with furan in benzene using $SnCl_4$, and (2) dry distillation of the silver salt of furilic acid. Later the product was prepared in better yield by the action of furylmagnesium bromide on furonitrile.[98] It has also been reported by Yamaguchi[111] who derived it from furfural oxime.

2-Furyl 2-pyrryl ketone: (furoylpyrrole): m.p. 69–70°; b.p. 141–144° (1.5 mm.); obtained in 42 per cent yield by reaction of furoyl chloride and pyrrylmagnesium iodide.[29]

2-Furyl 2-thienyl ketone: b.p. 134–136° (3 mm.); d_{23}^{23} 1.3004; n_D^{24} 1.6694; **semicarbazone,** m.p. 150°; formed in 66 per cent yield by furoylation of thiophene using furoyl chloride in the presence of $SnCl_4$.[29, 37]

2-Furyl 2,5-dimethyl-3-thienyl ketone: b.p. 180–182° (18 mm.); **semicarbazone,** m.p. 167°; from dimethylthiophene and furoyl chloride using $AlCl_3$. The ketone does not give the Elbs reaction.[30]

Diketones

1-Furyl-1,3-alkanediones. The compounds of this classification have been prepared by condensing furoic ester with methyl ketones (reaction 1) in the presence of sodium alkoxide or sodium amide. Highly acceptable product yields have been reported, notably in recent work using sodium amide suspended in ether.[112] However, when the methyl ketone is 2-furyl methyl ketone, attempted acylation with esters using this condensing agent (reaction 2) gives almost negligible yields of the appropriate 1,3-diketones.[112] Harris and Levine[112] attribute this to the formation of an ether-insoluble ketone-ammonia complex. Certainly such removal of ketone from the reaction medium would obviate its acylation. Since no similar phenomenon was observed with other ketones, however, including thienyl methyl ketone, it would appear that the interfering side-reaction may also involve the furan nucleus[a] rather than merely the carbonyl group. In this connection, sodium amide appears to be more drastic in its action than sodium alkoxides. Acylation of 2-furyl methyl ketone with oxalic ester in the presence of sodium ethoxide gives rise to furoylpyruvic ester in 32 per cent yield (p. 609). In a similar way sodium methoxide brings about condensation

[a] Possibly a nucleophilic attack at the 5-carbon atom. Compare with the action of alkalies and the Grignard reagent on 3-furyl ketones (p. 443) (see also p. 661).

[107] Pütter and Dilthey, *J. prakt. Chem.*, **149,** 183 (1937).
[108] Quint, Pütter and Dilthey, *Ber.*, **71,** 356 (1938).
[109] French and Smith, *J. Am. Chem. Soc.*, **67,** 1949 (1945).
[110] Freundler, *Bull. soc. chim.* (*3*), **17,** 609 (1897).
[111] Yamaguchi, *Bull. Chem. Soc. Japan*, **1,** 54 (1926); *C. A.*, **21,** 75 (1927).
[112] Harris and Levine, *J. Am. Chem. Soc.*, **71,** 1120 (1949).

with ethyl trifluoroacetate (reaction 2, R = CF_3) to give the appropriate 1,3-diketone in 70 per cent yield.[113]

In their study of acyl exchange reactions between esters and 1,3-diketones (reaction 3), McElvain and Weber[114] included furoic ester, and found that an acetyl group could be replaced by furoyl to give the appropriate furylalkanedione.

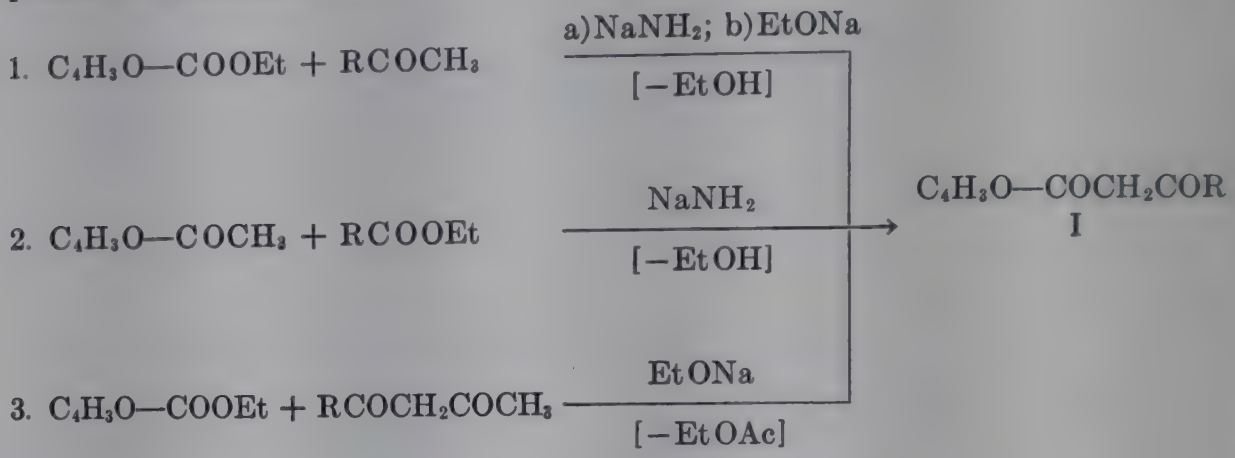
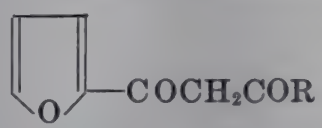


TABLE 9. 1-FURYL-1,3-ALKANEDIONES

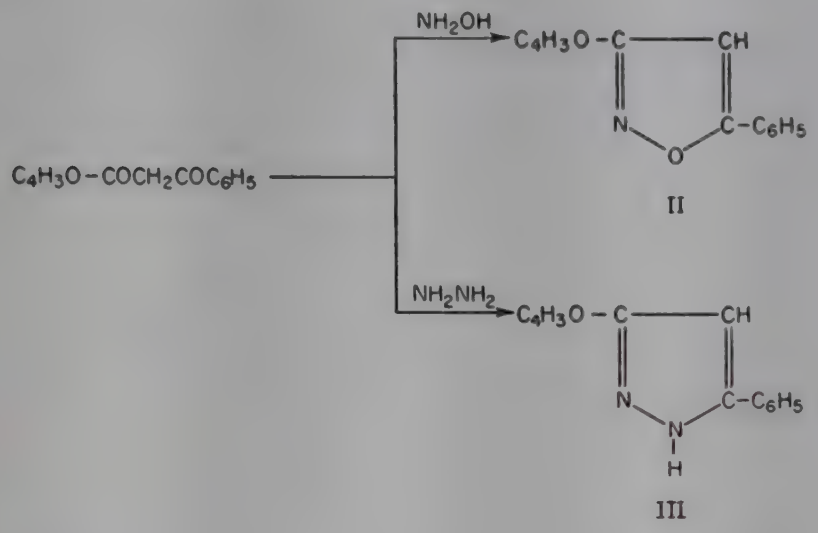


Compound	Physical constants and derivatives (°C.)	Preparation method	Yield (%)	Ref.
1-(2-Furyl)-1,3-butanedione (I, R = CH_3)	m.p. 30–31	1, a or 1, b	40–45	115, 116, 114, 112, see also 117
	b.p. 107–110 (10 mm.)	2	3.9	
	Cu chelate, m.p. 219–222	3	32*	
1-(2-Furyl)-4,4,4-trifluoro-1,3-butanedione (I, R = CF_3)	m.p. 19–21	2 (MeONa)	70	113
	dioxime, m.p. 152.7–153.5			
	Cu chelate, m.p. 226–228			
1-(2-Furyl)-5-methyl-1,3-hexanedione (I, R = i-C_4H_9)	b.p. 119–121 (4 mm.)	1, a	73.4	112
	Cu chelate, m.p. 93–97	2	3.6	
1-(2-Furyl)-1,3-octanedione (I, R = C_5H_{11})	b.p. 143–146 (7 mm.)	1, a	79.1	112
	Cu chelate, m.p. 97–101	2	1.9	
1-(2-Furyl)-3-phenyl-1,3-propanedione (I, R = C_6H_5)	m.p. 68–69	1, a	86.7	118, 116, 114, 112, 119, 80
	b.p. 165–169 (3 mm.)	1, b	55	
	monoxime, m.p. 137	2	5.4	
	dioxime, m.p. 168, 172	3	47	
	Cu chelate, m.p. 245–248			
1-(2-Furyl)-3-(2-thienyl)-1,3-propanedione (I, R = 2-thienyl)	m.p. 54.5–55.5	1, a	74.5	112
	b.p. 192–195 (6 mm.)			
	Cu chelate, m.p. 272–274			

* In addition, a 34% yield of 1,3-difuryl-1,3-propanedione was obtained (no constants given).[114]

[113] Reid and Calvin, *J. Am. Chem. Soc.*, **72**, 2948 (1950).
[114] McElvain and Weber, *J. Am. Chem. Soc.*, **63**, 2192 (1941).
[115] Kutz and Adkins, *J. Am. Chem. Soc.*, **52**, 4036 (1930).
[116] Sprague, Beckham and Adkins, *J. Am. Chem. Soc.*, **56**, 2665 (1934).
[117] Shalygin, *J. Gen. Chem. U. S. S. R.*, **15**, 375 (1945); *C. A.*, **40**, 3752 (1946).
[118] Semmler and Ascher, *Ber.*, **42**, 2355 (1909).
[119] Musante and Berretti, *Gazz. chim. ital.*, **79**, 683 (1949); *C. A.*, **44**, 4457 (1950).

1-(2-Furyl)-1,3-butanedione is cleaved entirely at the acetyl carbonyl group when subjected to hydrolysis with either ethanolic hydrogen chloride or dilute, aqueous sodium hydroxide.[120] 1-(2-Furyl)-3-phenyl-1,3-propanedione with hydroxylammonium chloride at reflux gives rise to 5-phenyl-3-(2-furyl)isoxazole, II (m.p. 81°); with hydrazine, 5-phenyl-3-(2-furyl)pyrazole, III (m.p. 173°).[119]



Miscellaneous.

1-(2-Furyl)-3-methyl-1,3-butanedione: $C_4H_3OCOCH(CH_3)COCH_3$; b.p. 135–138° (25 mm.); by alkylation of 1-furyl-1,3-butanedione with methyl iodide and sodium ethoxide. **Cu salt,** m.p. 165°.[117]

Furoylmesityl oxide: $C_4H_3OCOCH_2COCH{=}C(CH_3)_2$; no constants. By condensing ethyl furoate with mesityl oxide using sodium ethoxide. Greenish oil which could not be distilled without decomposition.[117]

1-Furyl-4,4-dimethyl-1,3,5-hexanetrione: $C_4H_3OCOCH_2COC(CH_3)_2{-}COCH_3$; b.p. 130–135° (15 mm.); from ethyl furoate and Me_2CAc_2 in the presence of sodium ethoxide.[117]

2,5-Diacylfurans.

2,5-Diacetylfuran: m.p. 94°; **oxime,** m.p. 187°. Obtained in yields varying from 20–50 per cent by the action of ketene on 2,5-bisfurylmercuric chloride.[121]

2,5-Dibenzoylfuran: m.p. 107°; **dioxime,** m.p. 213–214° (α); m.p. 243–245° (β); **bisphenylhydrazone,** m.p. 155–156°. In 96 per cent yield by condensation of 2,5-furandicarbonyl chloride with benzene using $AlCl_3$[38] (see also [122, 34]).

3-Furyl Ketones

Only two unsubstituted ketones of this type are known, namely, 3-furyl methyl ketone and 3-furyl isopropyl ketone. The former was derived from 3-furylmercuric chloride by the action of ketene.[121] The latter, also known

[120] Gilman, "Organic Chemistry," Vol. I, p. 849, New York, John Wiley and Sons (1938).

[121] Gilman, Wooley and Wright, *J. Am. Chem. Soc.*, **55**, 2609 (1933).

[122] Hill, *Am. Chem. J.*, **25**, 439 (1901).

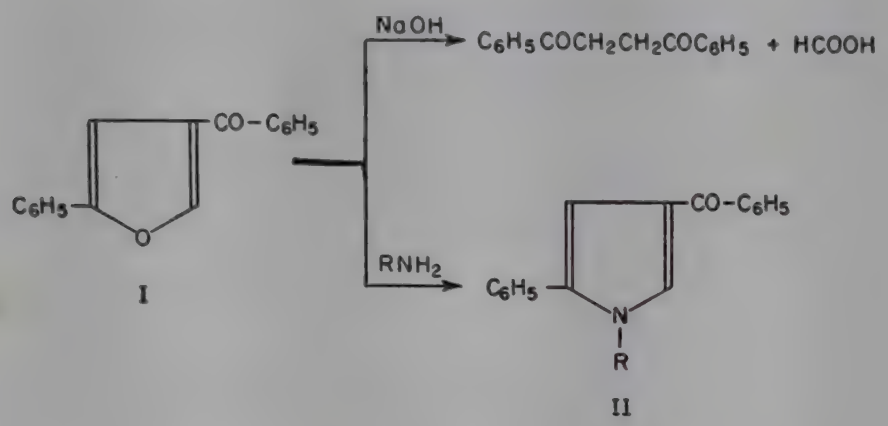
TABLE 10. ALKYL AND ARYL 3-FURYL KETONES

Ketone	Physical constants and derivatives (°C.)	Ref.
3-Furyl methyl	b.p. 84 (21 mm.) semicarbazone, m.p. 150	121
3-Furyl *i*-propyl	b.p. 90–100 (7 mm.) oxime, m.p. 66–67 semicarbazone, m.p. 93–94	123
2,5-Dimethyl-3-furyl methyl	b.p. 95 (23 mm.), 196 (760 mm.) oxime, m.p. 77–78 phenylhydrazone, m.p. 137	124, 125, 20, 22, 25, 11
2,5-Dimethyl-3-furyl ethyl	b.p. 105–108 (23 mm.) 2,4-dinitrophenylhydrazone, m.p. 171–172	11
2,5-Dimethyl-3-furyl propyl	b.p. 115–117 (23 mm.) 2,4-dinitrophenylhydrazone, m.p. 146–147	11
2-Methyl-5-phenyl-3-furyl methyl	m.p. 56–57 b.p. 179 (8 mm.) oxime, m.p. 111–112 semicarbazone, m.p. 251–252	126
2,5-Diphenyl-3-furyl methyl	m.p. 62–64 benzylidene deriv., m.p. 123	26
2,5-Di-*p*-bromophenyl-3-furyl methyl	m.p. 129–130	26
2,5-Diphenyl-3-furyl ethyl	m.p. 95.5–96	26
2,5-Dimethyl-3-furyl phenyl	b.p. 140 (15 mm.) d_{20}^{20} 1.152; n_D^{25} 1.5602	20
5-Phenyl-3-furyl phenyl	m.p. 113.7–114 oxime, m.p. 149.0–149.4	127, 128
2,5-Diphenyl-3-furyl phenyl	m.p. 76–77, 78–79 oxime, m.p. 173–176 semicarbazone, m.p. 225	106, 129, 130, 131
2-Methyl-5-mesityl-3-furyl mesityl	m.p. 202.5–203.5, 204	132
2-Methyl-4-phenyl-5-mesityl-3-furyl mesityl	m.p. 113	133

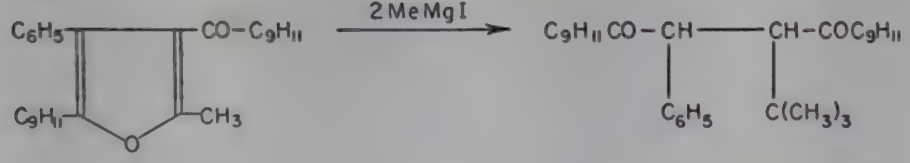
[123] Sebe, *J. Chem. Soc. Japan*, **64**, 1130 (1943); *C. A.*, **41**, 3785 (1947).
[124] Magnanini and Scheidt, *Gazz. chim. ital.*, **22, I**, 436 (1892).
[125] Magnanini and Bentivoglio, *Gazz. chim. ital.*, **24, I**, 433 (1894).
[126] March, *Compt. rend.*, **134**, 843 (1902); *Ann. chim. phys.* (7), **26**, 295 (1902).
[127] Fuson, Fleming and Johnson, *J. Am. Chem. Soc.*, **60**, 1994 (1938).
[128] Bailey and Lutz, *J. Am. Chem. Soc.*, **67**, 2232 (1945).
[129] Kleinfeller and Trommsdorff, *Ber.*, **71**, 2448 (1938).
[130] Lutz and Smith, *J. Am. Chem. Soc.*, **63**, 1148 (1941).
[131] Schmid, Hochweber and Halban, *Helv. Chim. Acta*, **30**, 423 (1947).
[132] Lutz, Reveley and Mattox, *J. Am. Chem. Soc.*, **63**, 3171 (1941).
[133] Lutz and Reveley, *J. Am. Chem. Soc.*, **63**, 3175 (1941).

as *Perilla* ketone, occurs naturally in the essential oil of *Perilla frutescens*.[128] For the most part the other products tabulated below were obtained by Friedel-Crafts acylation of the appropriately substituted furans, or by ring closure reactions from open chain types.

Studies involving several of the aryl 3-furyl ketones have revealed interesting behavior characteristics. For example, while 5-phenyl-3-furyl phenyl ketone, I, exhibits the anticipated high order of stability toward acid reagents, it is readily transformed by alkalies into 1,2-dibenzoylethane and formic acid; by ammonia to 5-phenyl-3-benzoylpyrrole (II, R = H); by aniline to the anil of 1,5-diphenyl-3-benzoylpyrrole (II, R = C_6H_5)[127] (see



also [125]). Additionally, 2-methyl-4-phenyl-5-mesityl-3-furyl mesityl ketone, III, is split by methylmagnesium iodide with formation of 1,4-dimesityl-2-*t*-butyl-3-phenyl-1,4-butanedione, IV.[134] Lutz[134] proposed a mechanism

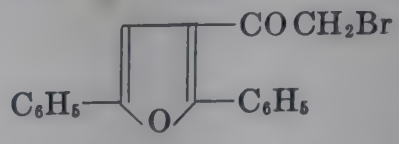


for this last reaction whereby the Grignard reagent adds 1,4 to the conjugated system made up of the carbonyl group and the 2,3-double bond of the furan nucleus. Further reaction of another mole of the Grignard with the intermediate so formed severs the link between the 2-carbon atom and the nuclear oxygen atom, and on hydrolysis, IV is obtained. The other reactions cited above may likewise be interpreted in terms of a nucleophilic attack on the 2-carbon atom (see Chapter 14), and future work may reveal this behavior to be quite general to 3-furyl ketones, perhaps differing only in degree depending upon such factors as the nature of the acyl group, the nature of other nuclear substituents of the ketone, and the relative donor tendency of the attacking reagent.

[134] Lutz and Reveley, *J. Am. Chem. Soc.*, **63**, 3178, 3180 (1941).

Haloalkyl 3-Furyl Ketones:

2,5-Diphenyl-3-furyl bromomethyl ketone:



m.p. 62–64°. Best obtained from 2,5-diphenyl-3-furoyl chloride by way of the diazomethyl ketone, m.p. 136.5–138°. Reduction with aluminum isopropoxide produces 2-bromo-1-(2,5-diphenyl-3-furyl)ethanol, m.p. 124–126°.[26]

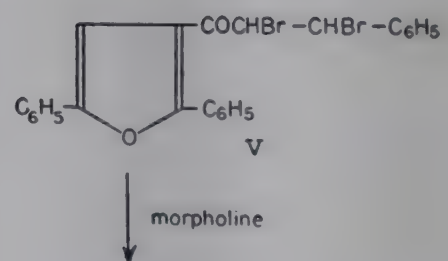
2,5-Di-*p*-bromophenyl-3-furyl bromomethyl ketone: m.p. 128–132°; as a crude product, difficult to purify, by the action of bromoacetyl chloride on 2,5-di-*p*-bromophenylfuran using aluminum chloride.[26]

2,5-Di-*p*-bromophenyl-3-furyl dibromomethyl ketone: m.p. 168.5°; in almost quantitative yield by treating the corresponding methyl ketone with bromine in carbon tetrachloride at room temperature. Also obtained in 83 per cent yield by similar bromination of the preceding compound.[26]

2,5-Diphenyl-3-furyl 1,2-dibromo-2-phenylethyl ketone, V (below): m.p. 180°. This is the dibromide of 2,5-diphenyl-3-furyl styryl ketone and is produced by the action of bromine on the latter.[26]

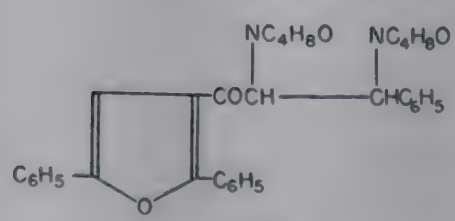
Aminoalkyl 3-Furyl Ketones

Condensation of 2,5-diphenyl-3-furyl bromomethyl ketone with diethylamine gives rise to the corresponding diethylaminomethyl ketone (hydrochloride, m.p. 202–204°).[26] In the same way, morpholine condenses with the dibromide, V, of 2,5-diphenyl-3-furyl styryl ketone to give the dimorpholino derivative, VI, m.p. 192°.[26] A number of amino ketones have also



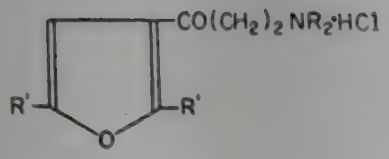
V

morpholine



VI

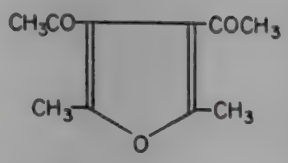
been prepared by means of the Mannich reaction starting with 2,5-dimethyl- and 2,5-diphenyl-3-furyl methyl ketones. These are tabulated below. Attempts to reduce them to the amino alcohols failed, whether by catalytic hydrogen or by the use of aluminum isopropoxide.[26] They possess little or no activity against avian malaria.[26]



R'	NR_2	m.p. (°C.)	Ref.
CH_3	$N(CH_3)_2$	175–177	(85)
C_6H_5	$N(CH_3)_2$	189	(26)
C_6H_5	$N(C_2H_5)_2$	147	(26)
C_6H_5	$N(n\text{-}C_4H_9)_2$	144	(26)
C_6H_5	$N(CH_3)CH_2C_6H_5$	193 (softens, 182)	(26)
C_6H_5	piperidyl	194–195	(26)
C_6H_5	morpholinyl	101.5 (free base)	(26)

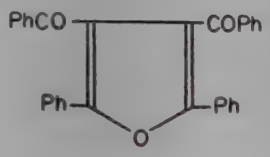
Miscellaneous

2,5-Dimethyl-3,4-diacetylfuran:

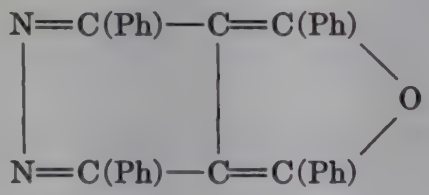


m.p. 63–64°; by cyclodehydration of *sym.*-tetracetylethane in concentrated hydrochloric or sulfuric acid.[135, 136, 137]

2,5-Diphenyl-3,4-dibenzoylfuran:

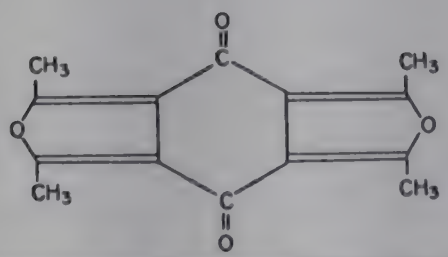


no constants; by ring closure of *sym.*-tetrabenzoylethane. Oxidative cleavage produces *sym.*-tetrabenzoylethylene. With hydrazine hydrate in acetic acid, the diketone is transformed into



m.p. 255°.[138]

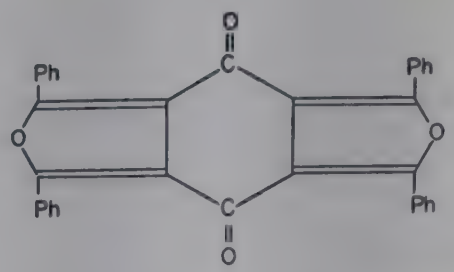
Uvinone:



[135] Zanetti, *Gazz. chim. ital.*, **23**, II, 299 (1893); *Chem. Centr.*, **1893**, II, 1050.
[136] Mulliken, *Am. Chem. J.*, **15**, 523 (1893).
[137] Trefil'ev and Livanov, *J. Gen. Chem. U. S. S. R.*, **11**, 182 (1941); *C. A.*, **35**, 7960 (1941).
[138] Keller and von Halban, *Helv. Chim. Acta*, **27**, 1253 (1944).

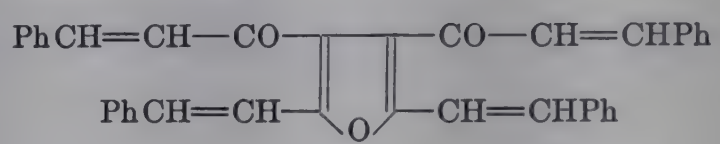
m.p. 247.5°; obtained along with 2,5-dimethyl-3-furoic acid and 2,5-dimethylfuran as products of the distillation of 2,5-dimethyl-3,4-furandicarboxylic acid (uvinic acid).[139]

Phenyluvinone:



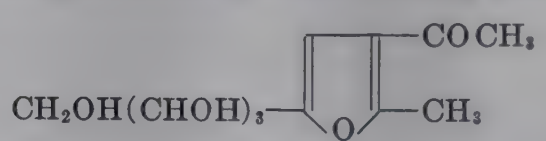
m.p. > 280°; as in the preceding case, starting with 2,5-diphenyl-3,4-furandicarboxylic acid.[140]

2,5-Distyryl-3,4-dicinnamoylfuran:



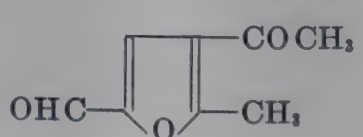
m.p. 168°; on heating 1,1,2,2-tetracinnamoylethane in glacial acetic acid.[141]

2-Methyl-5-(*d*-arabo-tetrahydroxybutyl)-3-furyl methyl ketone:



m.p. 152°; by condensation of glucose with acetylacetone in methanol in the presence of zinc chloride. **2,4-Dinitrophenylhydrazone,** m.p. 142°. On boiling in 10 per cent acetic acid, the ketone undergoes cleavage and recyclization to 7,8-*d*-erythro-dihydroxy-2-methyl-1,5,6,7,8,9-hexahydro-1,5-dioxa-3-naphthyl methyl ketone.[142]

5-Methyl-4-acetylfurfural:



m.p. 104–105°; by oxidation of the preceding compound using periodic acid.[142]

2-Furylalkanones

The products dealt with here are ketones in which the carbonyl is separated from the furan nucleus by one or more carbon atoms. The general structure of the class is 2-C_4H_3O—$(CRR')_nCOR''$, where R and R′ are H, alkyl or aryl, and R″ is alkyl or aryl. Those furans possessing two such substituent groups are also included.

The simplest member of the series, furylacetone, was first prepared by

[139] Dietrich and Paal, *Ber.*, **20**, 1077 (1887).
[140] Perkin and Schloesser, *J. Chem. Soc.*, **57**, 944 (1890).
[141] Swiderski, *Roczniki Chem.*, **20**, 54 (1946); *C. A.*, **42**, 1930 (1948).
[142] Jones, *J. Chem. Soc.*, **1945**, 116.

Darzens[145] by heating α-methyl-β-furylglycidic acid (see Chapter 13), and more recently by Hass[143] by hydrolysis of the oxime derived by reduction of furfurylidenenitroethane.

$$C_4H_3O{-}CH{=}C(NO_2)R \xrightarrow{Fe,\ HCl} C_4H_3O{-}CH_2C(NOH)R \xrightarrow{HOH} C_4H_3O{-}CH_2COR$$

Homologs of furylacetone have been obtained by the following procedures:

(1) Reduction of the furylalkenones (see p. 466).
(2) Action of the Grignard reagent on the furylalkenones (see p. 467).
(3) Hydrolysis of the appropriate β-keto esters in aqueous acidic medium (p. 605).
(4) Alkylation of the furylalkyl phenyl ketones by the action of sodium amide and alkyl halides.[144]

$$C_4H_3O{-}CH_2CH_2COC_6H_5 \xrightarrow{MeI,\ NaNH_2} C_4H_3O{-}CH_2CHMeCOC_6H_5 + C_4H_3O{-}CH_2CMe_2COC_6H_5$$

(5) Condensation of furan or 2-methylfuran with vinyl ketones. In the case of furan with its two α-hydrogens, two oxoalkyl groups can be introduced. (This reaction is discussed as an abnormal Diels-Alder reaction in Chapter 2).

Spectrographic studies involving several members of this class of ketones are reported by Kasiwagi[163] who further showed[162] (see also [158]) that they

[143] Hass, Susie and Heider, *J. Org. Chem.*, **15**, 8 (1950).
[144] Maxim, *Bull. soc. chim.* (*4*), **49**, 891 (1931).
[145] Darzens, *Compt. rend.*, **142**, 214 (1906).
[146] Erlenmeyer and Simon, *Helv. Chim. Acta*, **24**, 1210 (1941).
[147] Harries and Kaiser, *Ber.*, **32**, 1320 (1899).
[148] Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 90 (1926); *C. A.*, **20**, 3004 (1926).
[149] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).
[150] Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).
[151] Fujita, *J. Pharm. Soc. Japan*, **519**, 456 (1925); *C. A.*, **20**, 412 (1926).
[152] Van Campen and Johnson, *J. Am. Chem. Soc.*, **55**, 430 (1933).
[153] Fischer, Wiedemann and Robertson, *Ann.*, **520**, 52 (1935).
[154] Webb and Borcherdt, *J. Am. Chem. Soc.*, **73**, 752 (1951).
[155] Alder and Schmidt, *Ber.*, **76**, 183 (1943).
[156] Hoehn and Murbach, *J. Am. Chem. Soc.*, **72**, 4323 (1950).
[157] Maxim and Georgescu, *Bull. soc. chim.* (*5*), **3**, 1114 (1936).
[158] Chelintzev and Till, *Uchenye Zapiski Saratov. Gosudarst. Univ. im. N. G. Chernyshevskogo, Khim.*, **15**, 24 (1940); *C. A.*, **35**, 6953 (1941).
[159] Hunsdiecker, *Ber.*, **75**, 447 (1942).
[160] Nazarov and Nagibina, *Bull. acad. sci. U. R. S. S. Classe sci. chim.*, **1946**, 641; *C. A.*, **42**, 7736 (1948).
[161] Wienhaus and Leonhardi, *Ber. Schimmel and Co., Akt.-Ges.*, **1929**, 225; *C. A.*, **24**, 2127 (1930).
[162] Kasiwagi, *Bull. Chem. Soc. Japan*, **2**, 310 (1927); *C. A.*, **22**, 778 (1928).
[163] Kasiwagi, *Bull. Chem. Soc. Japan*, **1**, 233 (1926); *C. A.*, **21**, 1116 (1927).

TABLE 11. 2-FURYLALKANONES AND RELATED PRODUCTS

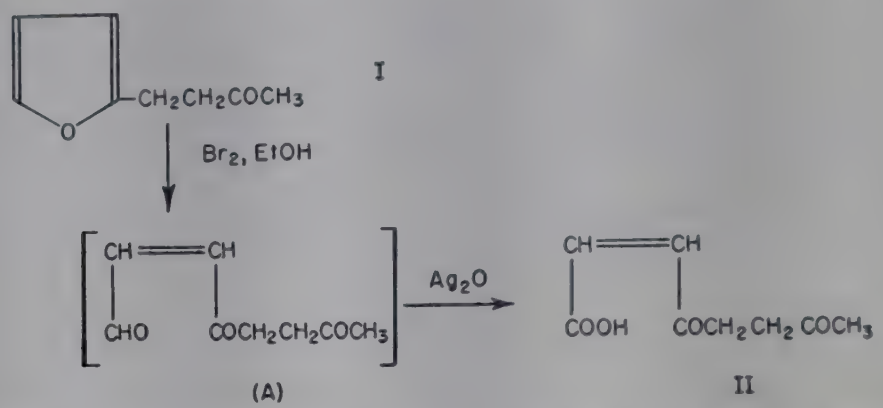
Formula (R = 2-C_4H_3O)	Preparation method	Physical constants and derivatives (°C.)	Ref.
RCH_2COCH_3	see text	b.p. 107 (10 mm.), 179–180 (—) oxime, b.p. 95 (5 mm.), 135–140 (25 mm.); m.p. 19–20 semicarbazone, m.p. 173–174	145, 143, 146
$RCH_2COC_2H_5$	see text	b.p. 76 (11–12 mm.), 99 (27 mm.) d_{25}^{25} 1.032; n_D^{25} 1.4680 oxime, b.p. 119–120 (10 mm.) d_{25}^{25} 1.082; n_D^{25} 1.4980	143
$RCH_2COC_3H_7$	see text	b.p. 95 (15 mm.) d_{25}^{25} 0.999; n_D^{25} 1.4629 oxime, b.p. 118 (4 mm.) d_{25}^{25} 1.054; n_D^{25} 1.4935	143
$RCH_2CH_2COCH_3$	1, 3, 5	b.p. 55 (1.5 mm.), 95 (15 mm.), 203 (atm.) d_4^{25} 1.0258; n_D^{25} 1.4729 oxime, b.p. 136–137 (120 mm.) semicarbazone, m.p. 143 *p*-bromophenylhydrazone, m.p. 103–104	147, 148, 149; see also 150, 146, 151, 152, 153, 154
2,5-CH_3—C_4H_2O—$CH_2CH_2COCH_3$	1, 5	b.p. 97–98 (12 mm.) semicarbazone, m.p. 132 2,4-dinitrophenylhydrazone, m.p. 140	155; see also 156
$RCH(C_2H_5)CH_2COCH_3$	2, 3	b.p. 95 (12 mm.), 120 (20 mm.) semicarbazone, m.p. 112	144, 157
$RCH(i\text{-}C_3H_7)CH_2COCH_3$	2	b.p. 115 (18 mm.) semicarbazone, m.p. 148	144
$RCH(C_3H_7)CH_2COCH_3$	2, 3	b.p. 113 (16 mm.), 115 (18 mm.)	144, 157

$RCH(i\text{-}C_4H_9)CH_2COCH_3$	2	b.p. 116 (18 mm.) semicarbazone, m.p. 100	187
$RCH(i\text{-}C_5H_{11})CH_2COCH_3$	2	b.p. 125–130 (—) d_{13} 0.9682; n^{13} 1.4808	158
$RCH(C_6H_5)CH_2COCH_3$	3	b.p. 160 (14 mm.) semicarbazone, m.p. 142	157
$RCH_2CH_2COC_2H_5$*	1	b.p. 88 (10 mm.), 206–208 (atm.) d_4^{25} 1.003; n_D^{25} 1.468	148, 149
$RCH_2CH(CH_3)COC_2H_5$	1	b.p. 93–100 (13 mm.) d_4^{25} 0.995; n_D^{25} 1.466	148
$2,5\text{-}CH_3—C_4H_2O—CH_2CH_2COC_3H_7$	1	b.p. 89–90 (1.5 mm.)	159
$2,5\text{-}CH_3—C_4H_2O—CH_2CH_2COCH=C(CH_3)_2$	5	m.p. 37–38 b.p. 123–124 (4 mm.) semicarbazone, m.p. 162	160
$2,5\text{-}CH_3—C_4H_2O—CH_2CH_2COCH_2CH(CH_3)_2$	reduction of preceding compound	b.p. 134–135 (20 mm.) d_4^{20} 0.9569; n_D^{20} 1.4640	160
$R(CH_2)_4COCH_3$	1	b.p. 93–95 (2 mm.) d_{20} 0.995; n_D^{20} 1.47023 semicarbazone, m.p. 121–122	161
$2,5\text{-}CH_3CO(CH_2)_2—C_4H_2O—(CH_2)_2COCH_3$	5	b.p. 130–135 (1.5 mm.), 174–176 (12 mm.) n_D^{25} 1.4849 bissemicarbazone, m.p. 181 bis-2,4-dinitrophenylhydrazone, m.p. 168	155, 154
$2,5\text{-}(CH_3)_2C=CHCO(CH_2)_2—C_4H_2O—(CH_2)_2COCH=C(CH_3)_2$	5	m.p. 78 bissemicarbazone, m.p. 141–142	160
$2,5\text{-}(CH_3)_2CHCH_2CO(CH_2)_2—C_4H_2O—(CH_2)_2COCH_2CH(CH_3)_2$	reduction of preceding compound	m.p. 62	160

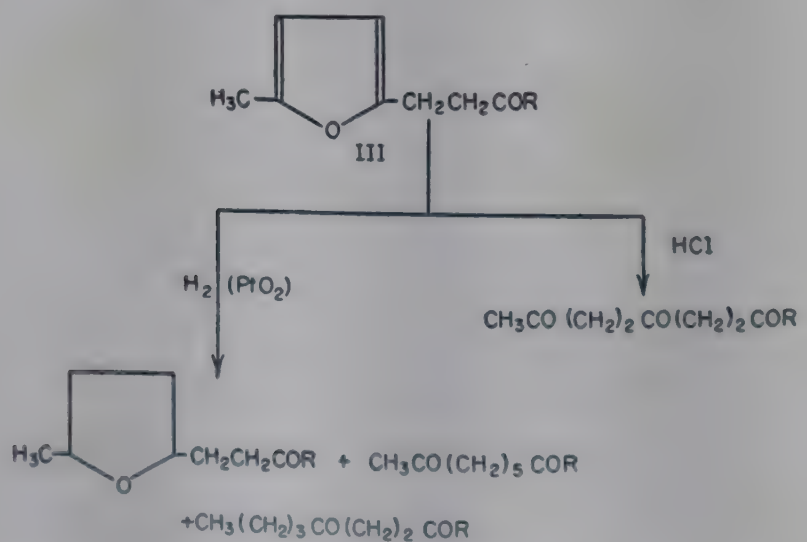
* Based on Kasiwagi,[162] this product would be formulated as the isomer, $C_4H_3O—CH_2CH(CH_3)COCH_3$. The correct formulation rests on the identity of the precursor derived from furfural and methyl ethyl ketone in basic solution (see p. 454).

react normally with organomagnesium halides to give tertiary alcohols. Previously (preparation method 4) it was shown that the hydrogen atoms adjacent to the carbonyl group can be replaced by alkyl groups by standard procedures.

Baeyer's oxidation technique (p. 589) has been applied to furfurylacetone, I, by Fujita.[164] Thus, alcoholic bromine attacks the nucleus to form the keto-aldehyde, A (not isolated) which on subsequent treatment with alkaline silver oxide gives rise to 4,7-dioxo-2-octenoic acid, II.



The (5-methyl-2-furyl)alkanones (III below, where R = alkyl) are readily cleaved to aliphatic triketones by heating with hydrochloric acid in alcohol.[155, 160] Similarly, the 2,5-bisoxoalkylfurans give rise to alkanetetraones.[155, 160] The nucleus may also be ruptured by reduction with hydrogen over platinum oxide.[155] While the corresponding phenone (III, R = C_6H_5) is more resistant to either mode of cleavage, and failed to respond under the mild conditions employed,[155] there is little doubt that more strenuous treatment would have been effective.



ω-(2,5-Diphenyl-3-furyl)acetophenone: (2,5-diphenyl-3-phenacylfuran); V, m.p 113°, 115–116°. Obtained by the action of concentrated hydriodic acid on *cis*- or *trans*

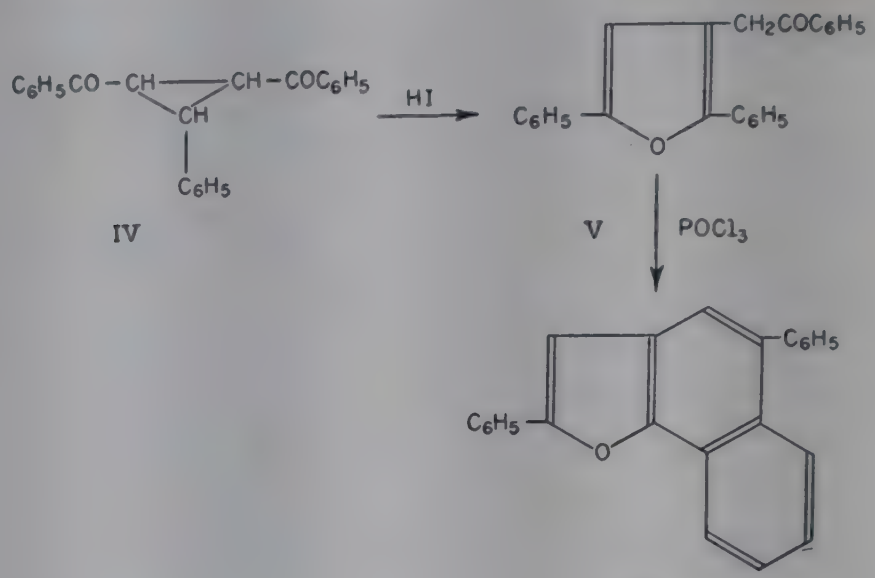
[164] Fujita, *J. Pharm. Soc. Japan*, **493**, 148 (1923); *C. A.*, **17**, 3030 (1923).

TABLE 12. FURYLALKYL ARYL KETONES

Formula (R = 2-C_4H_3O)	Method of preparation	Physical constants and derivatives (°C.)	Ref.
$RCH_2COC_6H_5$	see text	oxime, m.p. 90	167
2,5-CH_3—C_4H_2O—$CH_2CH_2COC_6H_5$	1, 5	b.p. 175–177 (13 mm.) 2,4-dinitrophenylhydrazone, m.p. 120	155
$RCH(CH_3)CH_2COC_6H_5$	2	—	168
$RCH(CH_3)CH_2COC_6H_4CH_3$-*p*	2	b.p. 170 (12 mm.) semicarbazone, m.p. 166	169
$RCH(C_2H_5)CH_2COC_6H_5$	2	—	168
$RCH(C_2H_5)CH_2COC_6H_4CH_3$-*p*	2	b.p. 175 (11 mm.) semicarbazone, m.p. 152	169
$RCH(C_2H_5)CH_2COC_6H_4(OCH_3)$-*p*	2	b.p. 218 (14 mm.) semicarbazone, m.p. 161	170
$RCH(C_2H_5)CH_2COC_6H_4Cl$-*p*	2	b.p. 197 (10 mm.) semicarbazone, m.p. 118	169
$RCH(C_2H_5)CH_2COC_6H_4Br$-*p*	2	b.p. 207 (10 mm.) semicarbazone, m.p. 138	169
$RCH(C_2H_5)CH(CH_3)COC_6H_5$	4	b.p. 178 (19 mm.)	144
$RCH(C_2H_5)C(CH_3)_2COC_6H_5$	4	b.p. 182 (23 mm.)	144
$RCH(C_2H_5)CH(C_2H_5)COC_6H_5$	4	b.p. 182 (18 mm.)	144
$RCH(C_2H_5)C(C_2H_5)_2COC_6H_5$	4	b.p. 176 (12 mm.)	144
$RCH(C_3H_7)CH_2COC_6H_5$	2	b.p. 190 (18 mm.)	144
$RCH(C_3H_7)CH_2COC_6H_4(OCH_3)$-*p*	2	b.p. 220 (12 mm.) semicarbazone, m.p. 149	170
$RCH(C_3H_7)CH_2COC_6H_4Cl$-*p*	2	b.p. 200 (10 mm.) semicarbazone, m.p. 122	170
$RCH(C_3H_7)CH_2COC_6H_4Br$-*p*	2	b.p. 215 (8 mm.) semicarbazone, m.p. 105	170
$RCH(C_3H_7)CH(CH_3)COC_6H_5$	4	b.p. 198 (28 mm.)	144
$RCH(C_3H_7)C(CH_3)_2COC_6H_5$	4	b.p. 205 (50 mm.)	144
$RCH(i\text{-}C_4H_9)CH_2COC_6H_5$	2	b.p. 191 (12 mm.) semicarbazone, m.p. 125	169, 170
$RCH(C_6H_5)CH_2COC_6H_5$	2	—	168
$RCH(C_6H_5)CH_2COC_6H_4CH_3$-*p*	2	b.p. 252 (19 mm.)	169
$RCH(C_6H_5)CH_2COC_6H_4Cl$-*p*	2	b.p. 242 (15 mm.) m.p. 79	170
$RCH(C_6H_5)CH_2COC_6H_4Br$-*p*	2	b.p. 268 (8 mm.) m.p. 78	170
$RCH(C_6H_5)CH(CH_3)COC_6H_5$	4	b.p. 222 (22 mm.)	144
$RCH(C_6H_5)C(CH_3)_2COC_6H_5$	4	b.p. 226 (22 mm.)	144
$RCH(C_6H_5)CH(C_2H_5)COC_6H_5$	4	b.p. 275 (78 mm.)	144

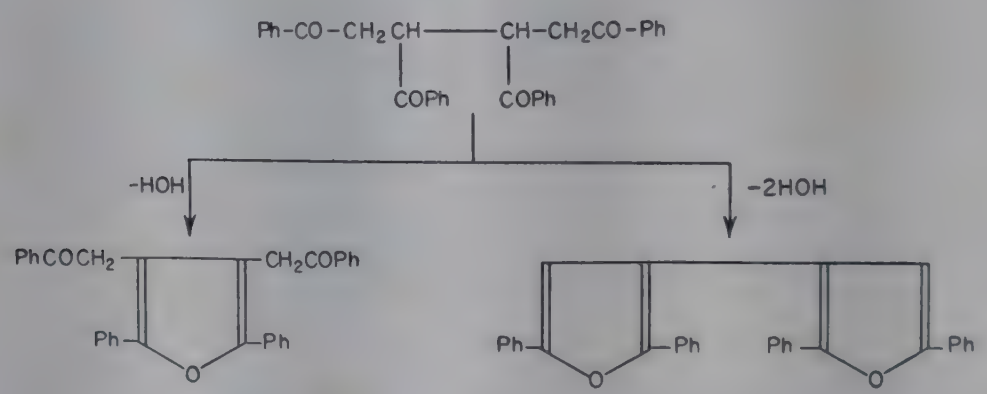
[167] Reichert and Kuhn, *Ber.*, **74**, 328 (1941).
[168] Maxim, *Bul. soc. chim. Romania*, **12**, 24 (1930); *C. A.*, **25**, 1520 (1931).
[169] Maxim and Angelesco, *Bull. soc. chim.*, **51**, 1365 (1932).
[170] Maxim and Angelesco, *Bull. soc. chim.* (*5*), **1**, 1128 (1934).

tribenzoylcyclopropane, IV[165]; also by ring closure of 1,4-diphenyl-2-phenacyl-1,4-butanedione.[166] With hydrazine hydrate V gives a **ketazine**, m.p. 214–215°, 219–220°. On warming V with phosphorus oxychloride it loses the elements of water, and cyclizes to the naphthofuran, VI, m.p. 120–121°.[165]



IV V VI

2,5-Diphenyl-3,4-diphenacylfuran: VII; m.p. 164–165°. Obtained in low yield along with a higher proportion of 3,3′-bis-2,5-diphenylfuran, VIII, m.p. 195–196°, as products of the cyclodehydration of 1,6-diphenyl-3,4-dibenzoyl-1,6-hexanedione.[166]



VII VIII

2-Furylalkenones and Related Products

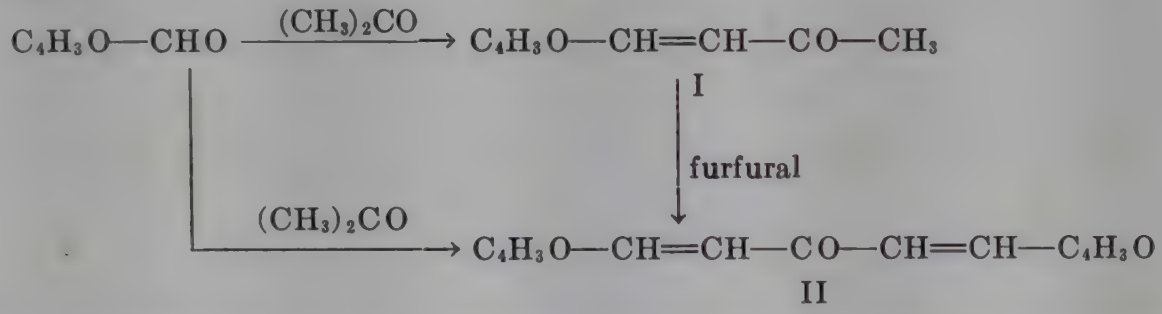
The compounds of this classification are the olefinic ketones in which one or more vinyl or substituted vinyl residue lies between the furan nucleus and the carbonyl group. For convenience, these have been divided into two general categories within which further subdivision has been made in tabulating the physical constants.

[165] Paal and Schulze, *Ber.*, **36**, 2425 (1903).
[166] Lutz and Palmer, *J. Am. Chem. Soc.*, **57**, 1947 (1935).

The Furylalkenones

Here are included all known compounds of the type 2,5-C_4H_2O—[R]-[$(CR{=}CR)_nCOR'$], where R represents hydrogen, alkyl or aryl and R′ is alkyl, aryl or a grouping similar to that indicated in the general structure as the other carbonyl substituent. They are readily obtained by condensing furfural or the alkylfurfurals with ketones containing the grouping —CH_2—CO—.

The best known member of the series is furfurylideneacetone, I, which was first reported by Schmidt,[171] and shortly thereafter by Claisen.[172, 173] The procedure involves condensation of furfural with acetone in aqueous alkaline medium, and when carried out at 10–15° using a two-fold excess of acetone the product has been isolated in 74 per cent yield.[174] Difurfurylideneacetone, II, which is formed as a by-product, is produced in almost quantitative yield when the ratio of reactants is one mole of acetone to two of furfural[148, 81, 173] (see also [175]), or by condensing furfural with furfurylideneacetone.[176] For the effect of varying the concentrations of alkali on the products of condensation of furfural with acetone, see Mangini and Andrisano,[177] Schmauss and Haberland[178] and Tikhonova.[178a] For the velocity of reaction of various aldehydes with acetone, see Chelintzev and Nikitin.[179]



With homologous methyl ketones, condensation with furfural might be

[171] Schmidt, *Ber.*, **14**, 1459 (1881).
[172] Claisen, *Ber.*, **14**, 2468 (1881).
[173] Claisen and Ponder, *Ann.*, **223**, 137 (1884).
[174] Hinz, Meyer and Schücking, *Ber.*, **76**, 676 (1943).
[175] Zerweck, "Furfural as a Starting Material for New Solvents and Plasticizers," PB No. **42436**, U. S. Dept. Commerce, 1940.
[176] Maxim and Copuzeanu, *Bul. soc. chim. Romania*, **16**, 117 (1934); *C. A.*, **29**, 4355 (1935).
[177] Mangini and Andrisano, *Ann. chim. applicata*, **34**, 4763 (1944); *C. A.*, **40**, 7694 (1946).
[178] Schmauss and Haberland, "Furfural Condensation," PB No. **739**, U. S. Dept. Commerce, 1943.
[178a] Tikhonova, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20**, 2213 (1950); *C. A.*, **45**, 7100 (1951).
[179] Chelintzev and Nikitin, *J. Gen. Chem. U. S. S. R.*, **10**, 1453 (1940); *Brit. Abstracts*, **A, II, 1941**, 329.

expected to give either the straight chain product, III, a branched chain type, IV, or both.

$$C_4H_3O—CHO \xrightarrow{CH_3COCH_2R} C_4H_3O—CH=CH—CO—CH_2R \text{ (III)} + C_4H_3O—CH=CR—CO—CH_3 \text{ (IV)}$$

When benzaldehyde condenses with such ketones, the reaction is reported to proceed with the formation of the analogous type III compounds if aqueous sodium hydroxide is the condensing agent, and to give those of type IV if hydrogen chloride is employed.[180, 181] Only basic condensing agents have been studied with furfural, and by analogy we should expect the straight chain products (III). They have been so formulated by most investigators, but for the reaction of furfural with methyl ethyl ketone in dilute caustic soda solution, Kasiwagi[162] (see also [182, 183]), suggested that IV ($R=CH_3$) is formed, a conclusion based on the fact that subsequent oxidation produced what appeared to be 2-methyl-3-(2-furyl)acrylic acid. The yield of acid was extremely poor, however, and at best can only be taken to show that some IV was present. On the other hand, treatment of the alkali-catalyzed condensation product of furfural and methyl ethyl ketone with alcoholic hydrogen chloride is reported to give 4,7-dioxononanoic acid.[b, 159, 184] If the structure of this acid is known with certainty, it must have had its origin in a ketone of structure III ($R=CH_3$), since IV ($R=CH_3$) would have produced the isomeric 4,7-dioxo-6-methyloctanoic acid. Pending further elucidation, the ketone in question has been assigned the structure III ($R=CH_3$).

The preceding types possessing a methylene group alpha to the carbonyl are capable of further condensation with aldehydes (furfural, benzaldehyde, etc.) to produce the corresponding dienones, as illustrated earlier for the particular case of difurfurylideneacetone. Vinylogous products, conjugated oxo-trienes, V, have been prepared by employing unsaturated aldehydes such as 3-(2-furyl)acrolein and cinnamaldehyde. When furylacrolein is reacted with aliphatic ketones in dilute, aqueous alkali, there is obtained a mixture of the expected unsaturated ketones (VI and VII).

[b] This interesting type of cleavage reaction which has been carried out with furfurylideneacetone and several of its homologs and with a number of the furfurylideneacetophenones is discussed elsewhere (see p. 653).

[180] Harries and Bromberger, *Ber.*, **35**, 3088 (1902).

[181] Stoermer and Wehln, *Ber.*, **35**, 3549 (1902).

[182] Haeussler and Brugger, *Ber.*, **77**, 152 (1944).

[183] Gutzatz, Russian Pat. 39,764 (1934); *C. A.*, **30**, 3591 (1936).

[184] Breusch and Ulusoy, *Rev. faculté sci. univ. Istanbul*, **13A**, 51 (1948); *C. A.*, **42**, 5850 (1948).

TABLE 13. FURFURYLIDENEACETONE AND ITS HOMOLOGS

Formula (R = 2-C_4H_3O)	Physical constants and derivatives (°C.)	Ref.
$RCH{=}CHCOCH_3$	m.p. 39.7 b.p. 116 (10 mm.) d_4^{45} 1.0572 oxime, m.p. 88–90 phenylhydrazone, m.p. 128–129, 131–132 *o*-tolylhydrazone, m.p. 83–85 *p*-tolylhydrazone, m.p. 187–188 *p*-chlorophenylhydrazone, m.p. 179–180 *p*-thiocyanophenylhydrazone, m.p. 143–143.5 *β*-naphthylhydrazone, m.p. 163–164 *o*-tolylsemicarbazone, m.p. 176–178	171, 172, 173, 185, 148, 186, 149, 187, 188, 189, 190, 191, 192, 177, 174, 184, 193, 194, 195, 81
2,5-CH_3—C_4H_2O—$CH{=}CHCOCH_3$	m.p. 35–36 b.p. 124 (12 mm.)	155
$RCH{=}CHCOC_2H_5$	b.p. 128 (15 mm.) d_4^{25} 1.0685; n_D^{25} 1.627 semicarbazone, m.p. 201.5–202.5	162, 149, 196, 184, 100, 183
$RCH{=}C(CH_3)COC_2H_5$	b.p. 135 (12 mm.) d_4^{25} 1.052; n_D^{25} 1.557 semicarbazone, m.p. 175–176	162, 100
$RCH{=}CHCO\text{-}n\text{-}C_3H_7$	b.p. 138–140 (15 mm.)	184
2,5—CH_3—C_4H_2O—$CH{=}CHCO\text{-}n\text{-}C_3H_7$	b.p. 138.5 (5 mm.)	159
$RCH{=}CHCO\text{-}i\text{-}C_3H_7$	b.p. 133–136 (18 mm.) d_4^{25} 1.0199; n_D^{25} 1.557	162, 100
$RCH{=}CHCO{-}CH_2{-}CH_2$ (with CH_2 bridge)	b.p. 137 (12 mm.)	198
$RCH{=}CHCO\text{-}n\text{-}C_4H_9$	b.p. 139–142 (14 mm.)	184
$RCH{=}CHCO\text{-}i\text{-}C_4H_9$	b.p. 115–116 (3 mm.), 130–135 (16 mm.) d_{20} 1.011; n_D^{20} 1.55282 semicarbazone, m.p. 175–176	161, 184, 196, 197
$RCH{=}CHCO\text{-}t\text{-}C_4H_9$	b.p. 120 (3 mm.) d_4^{25} 1.0022; n_D^{25} 1.548	162, 149
$RCH{=}CHCO\text{-}n\text{-}C_5H_{11}$	b.p. 140–145 (10 mm.)	184

$$R{-}CH{=}CH{-}CHO + R{-}CH{=}CHCOCH_3 \rightarrow \underset{V}{R{-}CH{=}CHCO(CH{=}CH)_2{-}R}$$

(R = 2—furyl)

$$\xrightarrow{(CH_3)_2CO} \underset{VI}{R{-}(CH{=}CH)_2COCH_3} + \underset{VII}{[R{-}(CH{=}CH)_2]_2CO}$$

With methyl vinyl ketone in methanolic sodium hydroxide, furylacrolein is converted into a liquid product, b.p. 174–176°(13 mm.) (semicarbazone, m.p. 106°), which is believed to be either 1-furyl-4-methoxymethyl-5-oxo-1,3-hexadiene, VIII, or the isomeric 1-furyl-5-oxo-7-methoxy-1,3-heptadiene, IX.[199] For the mechanism of formation of such types, see p. 416.

$$C_4H_3O{-}CH{=}CH{-}CHO + CH_3COCH{=}CH_2 + CH_3OH$$

$$\downarrow [NaOH]$$

$$C_4H_3O{-}CH{=}CH{-}CH{=}\overset{\displaystyle COCH_3}{\overset{|}{\underset{\displaystyle CH_2OCH_3}{\underset{|}{C}}}} \qquad C_4H_3O{-}CH{=}CH{-}CH{=}CH{-}COCH_2CH_2OCH_3$$

VIII IX

Furylalkendiones:

5-Furyl-4-pentene-2,3-dione: $C_4H_3O{-}CH{=}CH{-}CO{-}CO{-}CH_3$; m.p. 49°. Derived from the **monoxime**, m.p. 132°, obtained by condensation of furfural with

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[185] Auwers and Voss, *Ber.*, **42**, 4411 (1909).

[186] Leuck and Cejka, "Organic Syntheses," Collective Vol. I, p. 278, New York, John Wiley and Sons (1932).

[187] Maxim, *Bull. soc. chim.* (4), **49**, 887 (1931).

[188] Sah and Ma, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **1**, 259 (1932); *C. A.*, **27**, 3164 (1933).

[189] Surmin, *J. Gen. Chem. U. S. S. R.*, **5**, 1642 (1935); *C. A.*, **30**, 3430 (1936).

[190] Batty, Burawoy, Harper, Heilbron and Jones, *J. Chem. Soc.*, **1938**, 175.

[191] Kleene, *J. Am. Chem. Soc.*, **63**, 3538 (1941).

[192] Mangini and Andrisano, *Pubbl. ist. chim. ind. univ. Bologna*, **1943**, No. 1, 3; *C. A.*, **40**, 7694 (1946).

[193] Vogel, "Practical Organic Chemistry," p. 794, New York, Longmans, Green and Co. (1948).

[194] Sah and Lei, *Science Repts. Natl. Tsing Hua Univ.*, Ser. A, **2**, 1 (1933); Sah, Lei and Shen, *Ibid.*, **2**, 7 (1933); *C. A.*, **27**, 4222 (1933); Lei, Sah and Kao, *Ibid.*, **2**, 335 (1934); *C. A.*, **29**, 465 (1935); Lei, Sah and Shih, *J. Chinese Chem. Soc.*, **3**, 246 (1935); *C. A.*, **29**, 7298 (1935).

[195] Horii, *J. Pharm. Soc. Japan*, **56**, 53 (1936); *C. A.*, **30**, 4156 (1936).

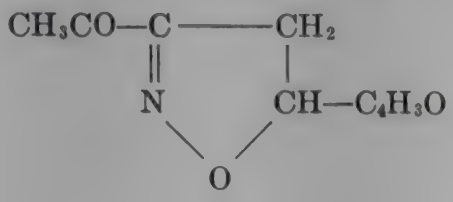
[196] Thurston (to American Cyanamid Co.), U. S. Pat. 2,372,233 (1945); *C. A.*, **39**, 5023 (1945).

[197] Wachs and Hedenburg, *J. Am. Chem. Soc.*, **70**, 2695 (1948).

[198] Hansen and Cassil (to California Spray-Chemical Corp.), U. S. Pat. 2,470,349 (1949); *C. A.*, **43**, 5530 (1949).

[199] Hinz and Laberenz, "On Some Furan Derivatives and Their Catalytic Hydrogenation," PB No. **19416**, U. S. Dept. Commerce, 1944.

biacetyl monoxime in aqueous potassium hydroxide[218] (see also [219]). Acetyl derivative of the monoxime, m.p. 141°. On refluxing in water, the monoxime cyclizes to form 5-furyl-3-acetyl-4,5-dihydroisoxazole,



m.p. 103–104°.[220]

1,6-Difuryl-1,5-hexadiene-3,4-dione: $(C_4H_3O—CH=CH—CO)_2$; m.p. 156–157°; from furfural and biacetyl in aqueous methanol in the presence of a small amount of piperidine acetate.[221]

Difurfurylidene-biacetyl and its vinylogs:

$$C_4H_3O—(CH=CH)_n—CO—CO—(CH=CH)_n—C_4H_3O$$

Compounds of this class, m.p. 156–157° (n = 1), m.p. 182–184° (n = 2); red-violet needles (n = 3) were prepared by condensing furfural, 3-(2-furyl)acrolein, and 5-(2-furyl)-2,4-pentadienal, respectively, with biacetyl in absolute alcohol in the presence of pyridine.[216]

6-Furyl-5-hexene-2,4-dione: [3-(2-furyl)acrylylacetone]:

$$C_4H_3O—CH=CH—CO—CH_2—CO—CH_3$$

m.p. 62–64°; from furylacrylylacetoacetic ester (p. 629). Introduction of a second furylacrylyl radical is accomplished by treating I with furylacrylyl chloride and

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[200] Minunni, *Gazz. chim. ital.*, **27**, II, 263 (1897).

[201] Cornubert and Phélisse, *Compt. rend.*, **227**, 1131 (1948); *Ibid.*, **229**, 460 (1949).

[202] Thurston (to American Cyanamid Co.), U. S. Pat. 2,373,152 (1945); *C. A.*, **39**, 4632 (1945).

[203] Claisen and Matthews, *Ann.*, **218**, 176 (1883).

[204] Knoevenagel, *Ber.*, **37**, 4038 (1904).

[205] Maxim and Copuzeanu, *Bull. soc. chim.* (*5*), **3**, 2251 (1936).

[206] Buck and Heilbron, *J. Chem. Soc.*, **121**, 1095 (1922).

[207] Maxim and Popescu, *Bull. soc. chim.* (*5*), **4**, 265 (1937).

[208] Röhmer, *Ber.*, **31**, 281 (1898).

[209] Maxim and Popescu, *Bull. soc. chim.* (*5*), **5**, 49 (1938).

[209a] Ponomarev, Til and Zelenkova, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20**, 1085 (1950); *C. A.*, **44**, 9403 (1950).

[210] Chelintzev and Kuznetsov, *J. Gen. Chem. U. S. S. R.*, **9**, 1858, 1901 (1939); *C. A.*, **34**, 4387 (1940).

[211] Rudchenko, *Uchenye Zapiski Kazan. Gosudarst. Univ.*, **100**, Book 1, No. 3, 135 (1940); *C. A.*, **37**, 4389 (1943).

[212] Haeussler and Dijkema, *Ber.*, **77**, 601 (1944).

[213] Umedzu, *Koryo Aromatics*, **12**, 24 (1950); *C. A.*, **45**, 2927 (1951).

[214] Bauer and Dieterle, *Ber.*, **44**, 2697 (1911).

[215] Giua, *Gazz. chim. ital.*, **47**, 86 (1917).

[216] Karrer, Cochand and Neuss, *Helv. Chim. Acta*, **29**, 1836 (1946).

[217] Stoll and Rouvé, *Helv. Chim. Acta*, **31**, 849 (1948).

[218] Diels and Sharkoff, *Ber.*, **46**, 1862 (1913).

[219] Diels, *Ber.*, **51**, 965 (1918).

[220] Diels and Roehling, *Ber.*, **51**, 828 (1918).

[221] Schlenk, *Chem. Ber.*, **81**, 175 (1948).

TABLE 14. FURYLALKADIENONES AND RELATED TYPES

Compound	Formula	Physical constants (°C.)	Ref.
Furfurylidenemethyl vinyl ketone (1-furyl-1,4-pentadien-3-one)	C_4H_3O—CH=CHCOCH=CH_2	b.p. 132–136 (8 mm.) **phenylhydrazone**, m.p. 139	199
Difurfurylideneacetone (1,5-difuryl-1,4-pentadien-3-one)	$(C_4H_3O$—CH=CH$)_2$CO	m.p. 57.5, 59, 60–61	172, 173, 200 148, 176, 177, 192, 201
1,5-Difuryl-2-methyl-1,4-pentadien-3-one	C_4H_3O—CH=C(CH_3)COCH=CHC_4H_3O	m.p. 60–61	162, 196, 202
1-Furfurylidene-3-benzylideneacetone (1-furyl-5-phenyl-1,4-pentadien-3-one)	C_4H_3O—CH=CHCOCH=CHC_6H_5	m.p. 55–56, 60	203, 173, 204
1-Furfurylidene-3-*p*-methylbenzylideneacetone	RCH=CHCOCH=CH$C_6H_4CH_3$-*p*	b.p. 237 (18 mm.) m.p. 85	205
1-Furfurylidene-3-*o*-hydroxybenzylideneacetone	C_4H_3O—CH=CHCOCH=CHC_6H_4(OH)-*o*	m.p. 162–163	206
1-Furfurylidene-3-anisylideneacetone	C_4H_3O—CH=CHCOCH=CH$C_6H_4(OCH_3)$-*p*	m.p. 84	176; see also 207
1-Furfurylidene-3-*p*-dimethylaminobenzylideneacetone	C_4H_3O—CH=CHCOCH=CH$C_6H_4[N(CH_3)_2]$-*p*	m.p. 178	176; see also 207
1-Furfurylidene-3-*o*-chlorobenzylideneacetone	C_4H_3O—CH=CHCOCH=CHC_6H_4Cl-*o*	m.p. 80	205
1-Furfurylidene-3-*o*-nitrobenzylideneacetone	C_4H_3O—CH=CHCOCH=CH$C_6H_4(NO_2)$-*o*	m.p. 104	205
1-Furfurylidene-3-*m*-nitrobenzylideneacetone	C_4H_3O—CH=CHCOCH=CH$C_6H_4(NO_2)$-*m*	m.p. 125	205
1-Furfurylidene-3-*p*-nitrobenzylideneacetone	C_4H_3O—CH=CHCOCH=CH$C_6H_4(NO_2)$-*p*	m.p. 159–160	205

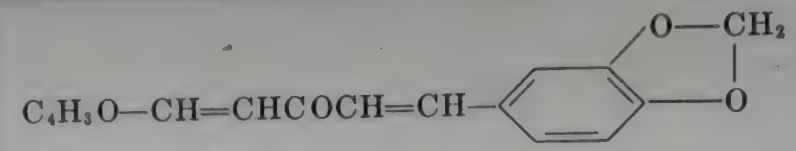
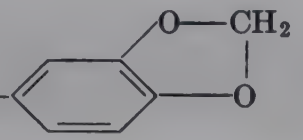
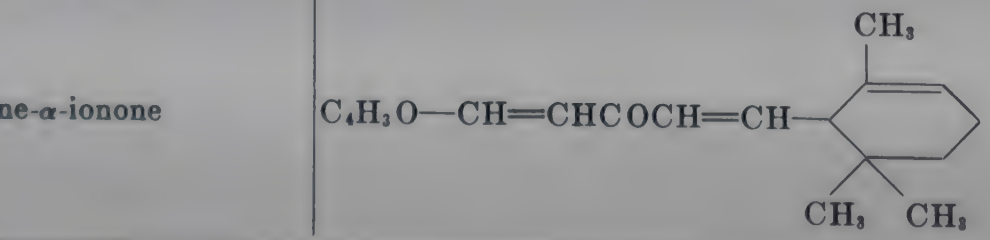
1-Furfurylidene-3-piperonylideneacetone		m.p. 132	176
5-Furyl-1-phenyl-2,4-pentadien-1-one (furylacroleinacetophenone)	C_4H_3O—(CH=CH)$_2$COC$_6$H$_5$	m.p. 52–53 **semicarbazone,** m.p. 59–60	208
5-Furyl-1-*p*-tolyl-2,4-pentadien-1-one	C_4H_3O—(CH=CH)$_2$COC$_6$H$_4$CH$_3$-*p*	m.p. 77	209
5-Furyl-4-methyl-1-tolyl-2,4-pentadien-1-one	C_4H_3O—CH=C(CH$_3$)—CH=CHCOC$_6$H$_4$CH$_3$	m.p. 107–108	209a
6-Furyl-3,5-hexadiene-2-one (furylacroleinacetone)	C_4H_3O—(CH=CH)$_2$COCH$_3$	m.p. 33–34, 35–36 **oxime,** m.p. 122–123 **phenylhydrazone,** m.p. 117.5–118	208, 209, 210, 211, 174
1-Furfurylidene-3-*i*-propylideneacetone (1-furyl-5-methyl-1,4-hexadien-3-one)	C_4H_3O—CH=CHCOCH=C(CH$_3$)$_2$	m.p. 140–145	189, 213
6-Furyl-3-methyl-3,5-hexadien-2-one	C_4H_3O—CH=CH—CH=C(CH$_3$)COCH$_3$	—	210; see also 212
1,7-Difuryl-1,4,6-heptatrien-3-one	C_4H_3O—(CH=CH)$_2$COCH=CHC$_4$H$_3$O	m.p. 65–70	211
7-Furyl-1-phenyl-1,4,6-heptatrien-3-one	C_4H_3O—(CH=CH)$_2$COCH=CHC$_6$H$_5$	m.p. 59–60	211
7-Furyl-1-*p*-dimethylaminophenyl-1,4,6-heptatrien-3-one	C_4H_3O—(CH=CH)$_2$COCH=CHC$_6$H$_4$[N(CH$_3$)$_2$]-*p*	m.p. 121	209

TABLE 14.—*Concluded*

Compound	Formula	Physical constants (°C.)	Ref.
7-Furyl-1-*p*-anisyl-1,4,6-heptatrien-3-one	$C_4H_3O—(CH=CH)_2COCH=CHC_6H_4(OCH_3)$-*p*	m.p. 99	209
7-Furyl-1-piperonyl-1,4,6-heptatrien-3-one		m.p. 119	209
1-Furyl-7-phenyl-1,4,6-heptatrien-3-one	$C_4H_3O—CH=CHCO(CH=CH)_2C_6H_5$	m.p. 96–97, 97–98	214, 215
1,9-Difuryl-1,3,6,8-nonatetraen-5-one (bisfurylacroleinacetone)	$[C_4H_3O—(CH=CH)_2]_2CO$	m.p. 121, 130	174, 209, 216; see also 210, 208
1-Furyl-9-phenyl-1,3,6,8-nonatetraen-5-one	$C_4H_3O—(CH=CH)_2CO(CH=CH)_2C_6H_5$	m.p. 103	209
1-Phenyl-9-furyl-1,4,6,8-nonatetraen-3-one	$C_4H_3O—(CH=CH)_3COCH=CHC_6H_5$	m.p. 110–111	209a
1,11-Difuryl-1,3,6,8,10-undecapentaen-5-one	$C_4H_3O—(CH=CH)_2CO(CH=CH)_3C_4H_3O$	m.p. 129	209
1,13-Difuryl-1,3,5,8,10,12-tridecahexaen-7-one	$C_4H_3O—(CH=CH)_3CO(CH=CH)_3C_4H_3O$	m.p. 175–176	216
Furfurylidene-α-ionone		b.p. 160–164 (0.025 mm.) $d_4^{18.5}$ 1.0407	217

sodium, giving rise to difurylacrylylacetone,

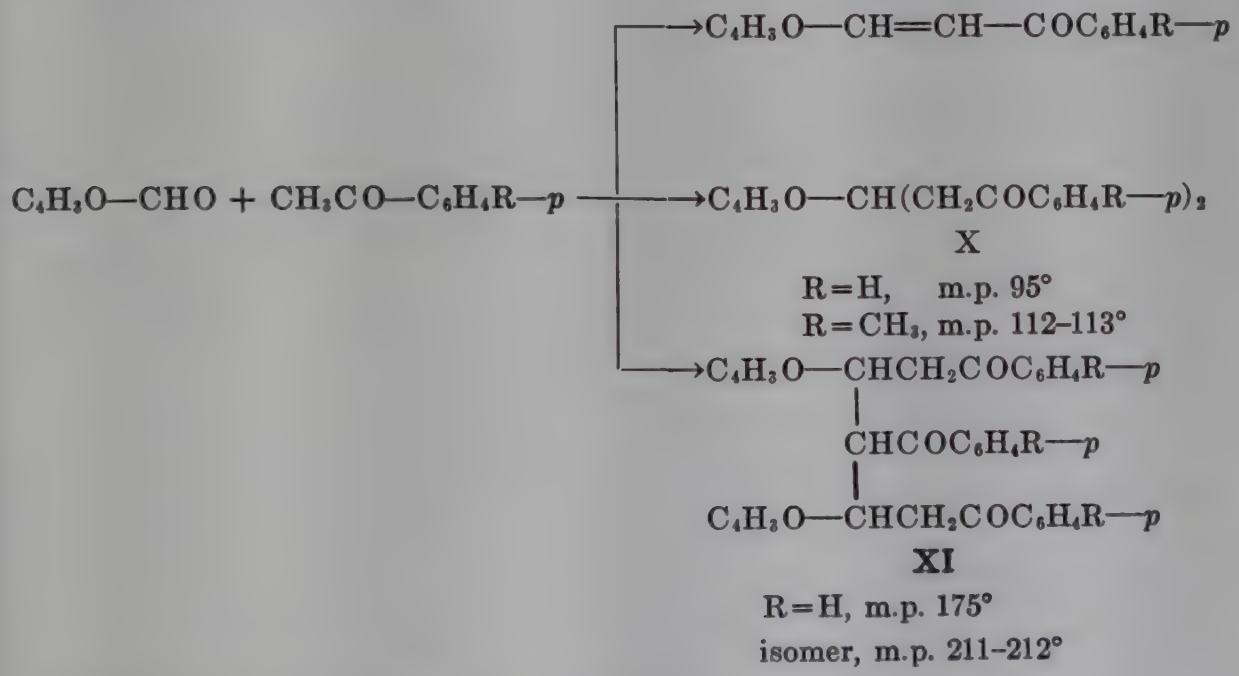
$$(C_4H_3O{-}CH{=}CH{-}CO)_2CH{-}CO{-}CH_3$$

m.p. 98–100°, from which is derived difurylacrylylmethane,

$$(C_4H_3O{-}CH{=}CH{-}CO)_2CH_2$$

m.p. 128–130°.[222]

Furfurylideneacetophenone has been obtained by the Friedel-Crafts reaction of β-2-furylacrylyl chloride with benzene.[33] More often it has been prepared by condensing equimolecular quantities of furfural and acetophenone in aqueous or aqueous-alcoholic sodium hydroxide. Using different molar ratios in the latter synthesis, it is possible to isolate 1,5-diphenyl-3-furyl-1,5-pentanedione (X) and 1,7-diphenyl-3,5-difuryl-4-benzoyl-1,7-heptanedione (XI).[223] Similar results have been obtained by reacting furfural with *p*-methylacetophenone[223] and with cinnamylideneacetone.[215] For the alkali-catalyzed condensation of furfural with methyl pyrryl ketones, see Finzi and Vecchi.[224]



Furfurylidene-2-acetylthiophene: (furylacrylylthiophene);

$$C_4H_3O{-}CH{=}CH{-}CO{-}C_4H_3S$$

polymorphic modifications, m.p. 71, 54, 53°; from furfural and acetylthiophene.[79]
Furfurylidene-2-acetylpyrrole: (furylacrylylpyrrole);

$$C_4H_3O{-}CH{=}CH{-}CO{-}C_4H_4N$$

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[222] Lampe, Rozenblumowna and Kessel, *Chem. Listy*, **26**, 454 (1932); *C. A.*, **27**, 721 (1933).

[223] Kostanecki and Podrajansky, *Ber.*, **29**, 2248 (1896).

[224] Finzi and Vecchi, *Gazz. chim. ital.*, **47, II**, 10 (1917); *Chem. Centr.*, **1918, II**, 277.

TABLE 15. FURFURYLIDENEACETOPHENONES AND RELATED PRODUCTS

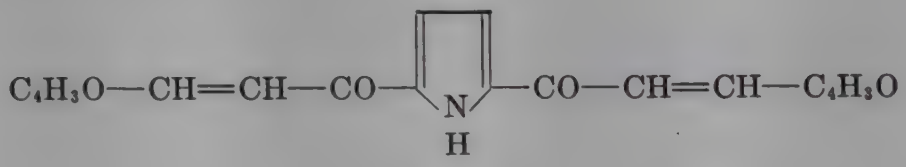
Compound	Physical constants (°C.)	Ref.
Acetophenones		
Furfurylidene	m.p. 26, 29 b.p. 179 (7 mm.), 319 (764 mm.) d_4^{17} 1.15 **oxime,** m.p. 82–83 for polymorphic modifications, see[79]	223, 118, 225, 168, 33, 100, 80, 79
(5-Methylfurfurylidene)	m.p. 66; b.p. 200 (12 mm.)	155
Furfurylidene-*p*-methyl	m.p. 67; b.p. 300 (—)	223, 33, 169
Furfurylidene-*p*-ethyl	m.p. 51–52	226
Furfurylidene-*p*-isopropyl	m.p. 63–64	226
Furfurylidene-*p*-*sec*-pentyl	b.p. 185 (3 mm.) n_D^{25} 1.6731	226
Furfurylidene-*p*-cyclohexyl	m.p. 119–120	226
Furfurylidene-*p*-phenyl	m.p. 137–139	226
Furfurylidene-*p*-chloro	m.p. 110, 78	227, 169
Furfurylidene-*p*-bromo	m.p. 81	169, 33
Furfurylidene-*o*-hydroxy	m.p. 79–80, 80–81 b.p. 210–217 (16–18 mm.)	225, 33
Furfurylidene-*m*-methoxy	m.p. 38.5–39.5 b.p. 175 (0.45 mm.) **2,4-dinitrophenylhydrazone,** m.p. 190–191	228
Furfurylidene-*p*-methoxy	m.p. 75, 79	170, 33, 229
Furfurylidene-*m*-nitro	m.p. 100–101	226
Furfurylidene-(2-hydroxy-4-methoxy)	m.p. 112	230, 227, 231
Furfurylidene-(2-hydroxy-5-methoxy)	m.p. 75	230
Furfurylidene-(3,4-dimethoxy)	m.p. 81	232; see also 233
Furfurylidene-(2-hydroxy-3,4-dimethoxy)	m.p. 105	233, 234
Furfurylidene-(2-hydroxy-4,5-dimethoxy)	m.p. 128	234
Furfurylidene-(6-chloro-4-methoxy-3-methyl)	m.p. 78–79	228
Related types		
Furfurylidene-2-acetonaphthone	m.p. 91	232
Furfurylidene-(1-hydroxy-2-acetonaphthone	m.p. 121–122 **1-acetoxy derivative,** m.p. 116–117	235
Furfurylidene-(4-methoxy-1-acetonaphthone)	m.p. 80–82	226
Furfurylidene-(6-methoxy-2-acetonaphthone)	m.p. 113	232

TABLE 15.—*Continued*

Compound	Physical constants (°C.)	Ref.
Furfurylidene-(1-hydroxy-4-bromo-2-acetonaphthone)	m.p. 154–155	236
ω-Furfurylidene-(3-methyl-5,6,7,8-tetrahydro-2-acetonaphthone)	m.p. 69–72 b.p. 248 (15 mm.)	237
Difurfurylidene-(2-nitro-4,6-diacetylresorcinol)	m.p. 262–265	238

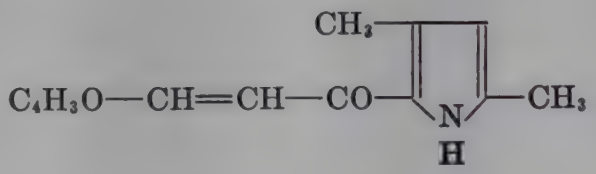
m.p. 134–135°; from furfural and methyl pyrryl ketone in boiling alcohol in the presence of sodium hydroxide.[224]

Difurfurylidene-2,5-diacetylpyrrole:



m.p. 229°; from furfural and 2,5-diacetylpyrrole in alcohol with sodium hydroxide.[224]

Furfurylidene-2-acetyl-3,5-dimethylpyrrole:

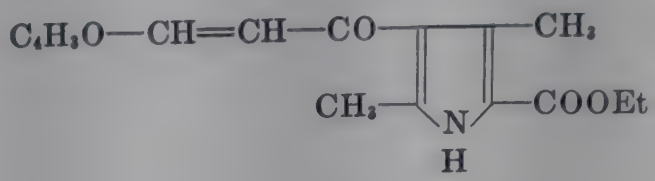


m.p. 181–182°. The **4-carbethoxy derivative,** m.p. 184–185°. The **4-acetyl derivative,** m.p. 170°.[224]

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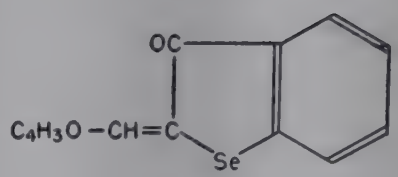
[225] Drake and Gilbert, *J. Am. Chem. Soc.*, **52,** 4965 (1930).
[226] Turner, *J. Am. Chem. Soc.*, **71,** 612 (1949).
[227] Otsuka, *J. Chem. Soc. Japan*, **65,** 539 (1944); *C. A.*, **41,** 3797 (1947).
[228] Martin and Robinson, *J. Chem. Soc.*, **1943,** 497.
[229] Robinson and Todd, *J. Chem. Soc.*, **1939,** 1743.
[230] Courant and Kostanecki, *Ber.*, **39,** 4031 (1906).
[231] Bargellini and Martegiani, *Gazz. chim. ital.*, **42, II,** 427 (1912).
[232] Robinson, *J. Chem. Soc.*, **1938,** 1390.
[233] Pfeiffer and Emmer, *Ber.*, **53,** 945 (1920); *C. A.*, **14,** 3412 (1920).
[234] Marini-Bettolo, *Gazz. chim. ital.*, **71,** 635 (1941); *C. A.*, **37,** 123 (1943).
[235] Alperin and Kostanecki, *Ber.*, **32,** 1037 (1899).
[236] Torrey and Brewster, *J. Am. Chem. Soc.*, **35,** 426 (1913).
[237] Butenandt, Dannenberg and Dresler, *Z. Naturforsch.*, **4b,** 69 (1949); *C. A.*, **44,** 3966 (1950).
[238] Algar and MacDonnell, *Proc. Roy Irish Acad.*, **38B,** 171 (1929).

Furfurylidene-3-acetyl-2,4-dimethyl-5-carbethoxypyrrole:



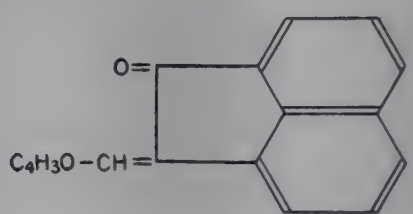
m.p. 149–150°.[224]

2-Furfurylidene-3-selenonaphthenone:



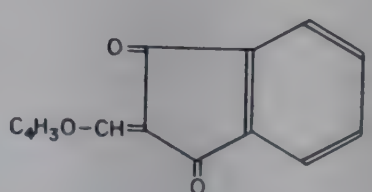
m.p. 145–147°; by condensation of furfural with 3-selenonaphthenol under the influence of a catalytic amount of hydrochloric acid.[239]

2-Furfurylidene-1-acenaphthenone:



m.p. 142–143°; from furfural and 1-acenaphthenone under the influence of sodium hydroxide.[240]

2-Furfurylidene-1,3-indanedione:



m.p. 209–210°; by heating furfural with 1,3-indanedione. Treatment with

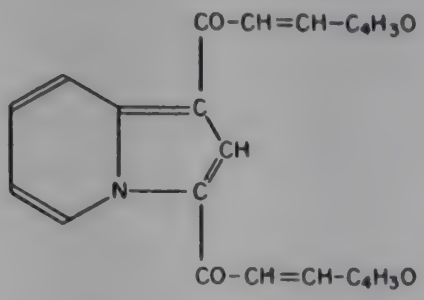
$$CH_3C(NH_2)=CHCOOEt$$

produces ethyl 1-furyl-3-methyl-1,4-dihydro-4-azafluoren-9-one-2-carboxylate, m.p. 249–251°, which on oxidation with chromic oxide gives ethyl 1-furyl-3-methyl-4-azafluoren-9-one-2-carboxylate, m.p. 141–142°.[241]

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[239] Lesser and Weiss, *Ber.*, **46**, 2640 (1913).
[240] de Fazi, *Gazz. chim. ital.*, **54**, 658 (1924); *C. A.*, **19**, 821 (1925).
[241] Petrov, Saper, and Sturgeon, *J. Chem. Soc.*, **1949**, 2134.

Difurfurylidenepicolide: (difurfurylidene-1,3-diacetylpyrrocoline);



m.p. 210°; from furfural and picolide in alcoholic alkali.[242]

The furylalkenones form unstable color bodies in aqueous hydrochloric or sulfuric acids[243, 244, 245] (see also [173]), and when treated with antimony trichloride in chloroform.[246] Extended heating with aqueous acids produces high melting resinous tars. The color formed by furfurylideneacetone in sulfuric acid has been employed for the determination of furfural[247] (see also [248]). An interesting, but difficultly reproducible analytical method for furfural consists in precipitating furfurylideneacetone by the action of potassium hydroxide, and comparing the rate of formation of precipitate with that from a standard solution of the aldehyde. With solutions containing from 0.01 to 0.20 per cent furfural, an accuracy of ±0.5 per cent is reported[249] (see also [250]).

The violet-red color obtained by dissolving difurfurylideneacetone in 60 per cent sulfuric acid is discharged by the addition of aliphatic aldehydes, a result attributed to replacement of the furfurylidene radical by the corresponding alkylidene group[251, 252] (see also [253]).

For studies relating to eutectic mixtures involving mono- and difurfurylideneacetone and phenolic compounds, see Chelintzev and Kuznetsov.[254]

Dry hydrogen chloride adds to difurfurylideneacetone with formation

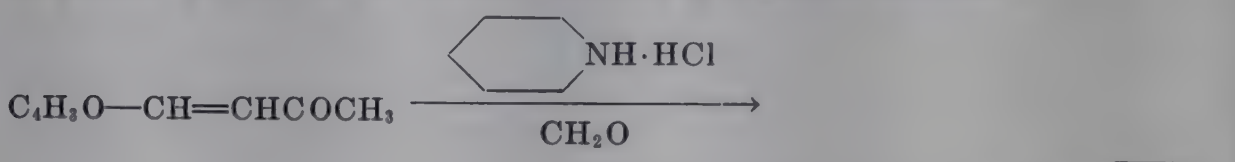
[242] Scholtz, *Ber.*, **45**, 734 (1912).
[243] Stobbe and Haertel, *Ann.*, **370**, 99 (1909).
[244] Chelintzev and Nikitin, *J. Gen. Chem. U. S. S. R.*, **5**, 256 (1935); *C. A.*, **29**, 5110 (1935).
[245] Chelintzev, *Bull. soc. chim.*, **6**, 70 (1939).
[246] Levine and Richman, *J. Biol. Chem.*, **101**, 373 (1933).
[247] Chelintzev and Nikitin, *Bull. soc. chim.* (*5*), **1**, 184 (1934).
[248] Nikitin and Tikhonova, *J. Applied Chem. U. S. S. R.*, **11**, 347 (1938); *C. A.*, **32**, 5721 (1938).
[249] Nikitin, *J. Applied Chem. U. S. S. R.*, **9**, 956 (1936); *C. A.*, **30**, 7496 (1936).
[250] Nikitin, *J. Gen. Chem. U. S. S. R.*, **7**, 9 (1937); *C. A.*, **31**, 4232 (1937).
[251] Chelintzev and Nikitin, *J. Gen. Chem. U. S. S. R.*, **7**, 2324 (1937); *C. A.*, **32**, 549 (1938).
[252] Chelintzev and Nikitin, *Bull. soc. chim.*, **51**, 875 (1932).
[253] Chelintzev, *Bull. soc. chim.* (*5*), **3**, 1035 (1936).
[254] Chelintzev and Kuznetsov, *Bull. soc. chim.*, **6**, 256 (1939).

of violet colored salts of variable composition,[243] and to furfurylideneacetophenone to give a hydrochloride, m.p. 46°.[33]

The halochromism of the furfurylideneacetophenones and of the furyl aryl ketones is discussed by Maxim and Popesco.[33]

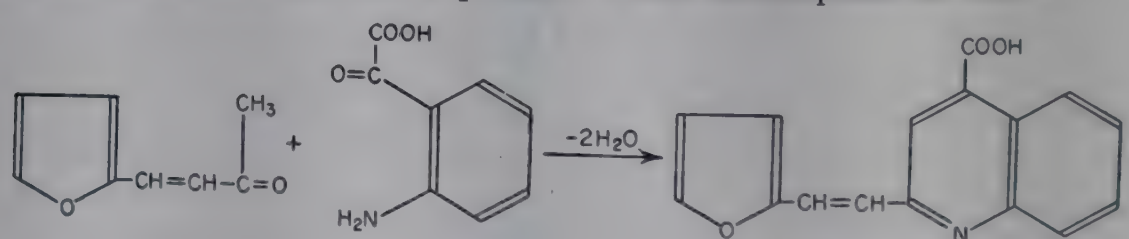
Oxidation of furfurylideneacetone with hypochlorites to produce 3-(2-furyl)acrylic acid is discussed elsewhere (p. 618). With nitric acid, oxidation proceeds violently, and from the reaction mixture, oxalic acid and ammonium tetroxalate have been isolated.[255]

The Mannich reaction with furfurylideneacetone proceeds in the normal fashion, a hydrogen atom of the methyl group being replaced by an aminomethyl radical. Thus, condensation with piperidine hydrochloride and formaldehyde gives 1-furyl-5-piperidino-1-penten-3-one, XII (hydrochloride m.p. 192°).[256] Dimethyl- and diethylamine hydrochlorides have also been employed, giving rise to the corresponding β-amino ketones.[256]



XII

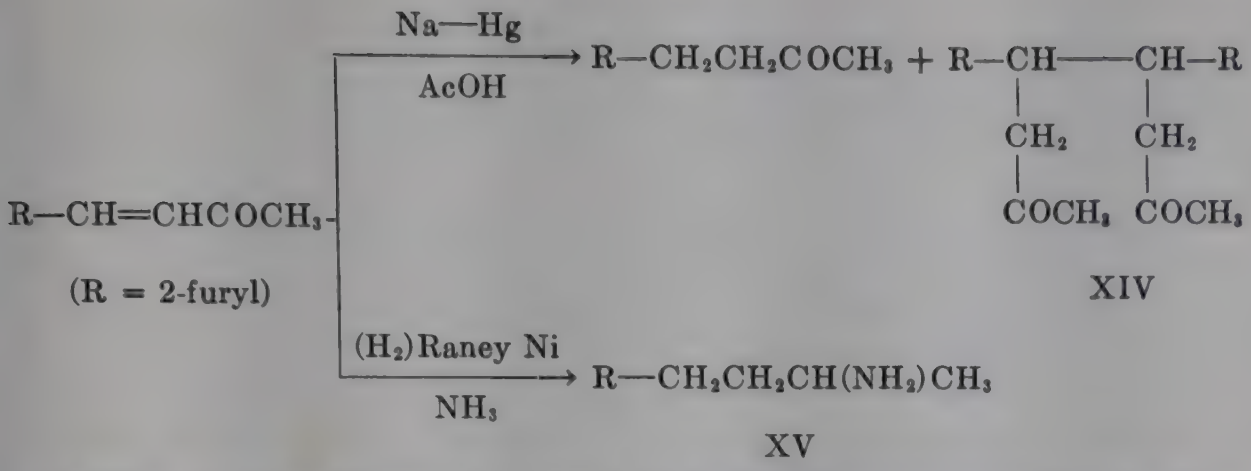
Condensation with isatin produces 2-furfurylidenequinoline-4-carboxylic acid, XIII, a brownish-yellow product which decomposes at 249°.[257]



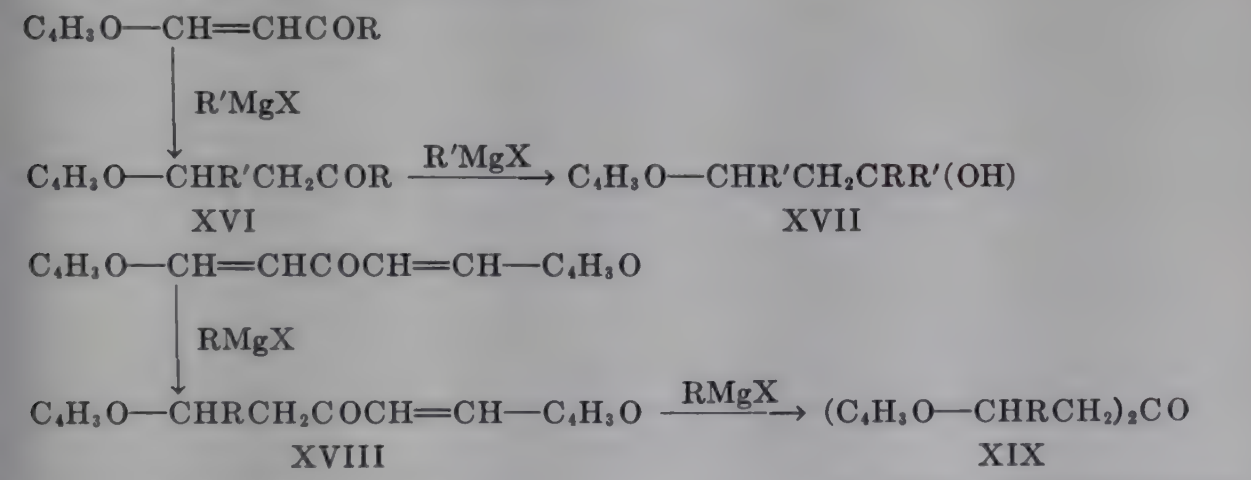
XIII

Many of the addition reactions common to α,β-unsaturated ketones have been carried out with the appropriate furylalkenones. On reduction, hydrogen adds first to the olefinic linkage to give the alkanones described earlier (p. 446). This has been accomplished by catalytic hydrogenation, and by the use of sodium in alcohol, or sodium amalgam in acetic acid. By the last procedure, some dimerization may occur as shown by the isolation of 4,5-difuryl-2,7-octanedione, XIV, as a minor product of the reduction of furfurylideneacetone[147] (see also [163, 151]). Aminative reduction over Raney nickel has been carried out by Haskelberg[258] who isolated 4-furyl-2-butylamine, XV, as the product.

[255] Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 1646 (1933).
[256] Nisbet and Gray, *J. Chem. Soc.*, **1933**, 839.
[257] Johns and Kahl, *J. prakt. Chem.*, **118**, 14 (1928).
[258] Haskelberg, *J. Am. Chem. Soc.*, **70**, 2811 (1948).



Addition of the Grignard reagent to furfurylideneacetone[187, 158] and to the furfurylideneacetophenones,[168, 169, 170] proceeds first by 1,4-addition so that subsequent hydrolysis and ketonization produces the appropriate aliphatic ketone,[c] XVI (see Tables 11 and 12). On further reaction organomagnesium halides add 1,2- to the carbonyl group of XVI with formation of the carbinol, XVII (see Chapter 7). Difurfurylideneacetone behaves similarly, and in this way Maxim and Popescu[207] were able to prepare products of the general type XVIII and XIX. With benzylidenefurfurylideneacetone and related types, these workers report that the initial attack of the Grignard reagent is on the conjugated system comprising the carbonyl group and the double bond nearest the aromatic nucleus, so that hydrolysis gives rise to product XX.



R = C_2H_5; b.p. 199° (20 mm.)
semicarb., m.p. 76°

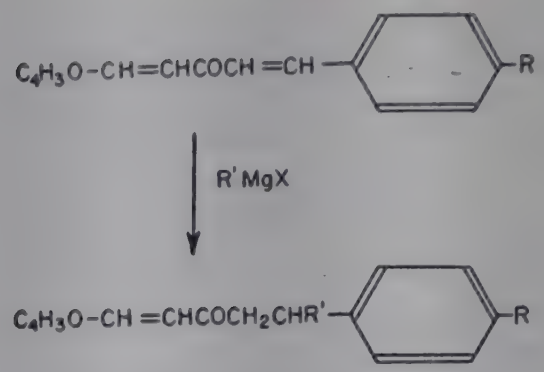
R = C_3H_7; b.p. 200° (16 mm.)
oxime, m.p. 90°

R = *i*—C_4H_9; b.p. 205° (15 mm.)
semicarb., m.p. 65°

R = phenyl; b.p. 220–240° (16 mm.)

R = C_3H_7; b.p. 200° (18 mm.)

[c] With acetylenebismagnesium bromide,[259] and with lithium acetylide in liquid



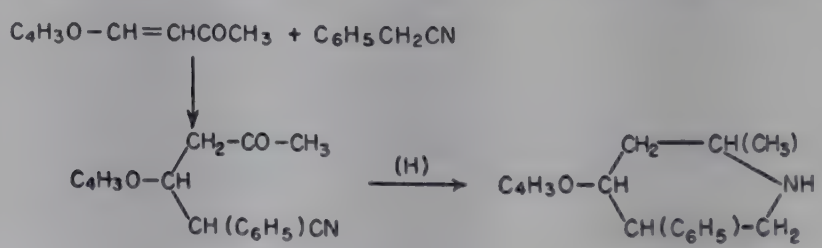
XX

XX

R = H; R′ = C_3H_7; m.p. 33°; b.p. 219° (18 mm.)
semicarb., m.p. 42°
R = $(CH_3)_2N$; R′ = C_2H_5; b.p. 253° (13 mm.)
semicarb., m.p. 66°
R = $(CH_3)_2N$; R′ = *i*—C_4H_9; m.p. 59°
semicarb., m.p. 192°
R = $(CH_3)_2N$; R′ = *i*—C_5H_{11}; b.p. 266° (13 mm.)
semicarb., m.p. 60°

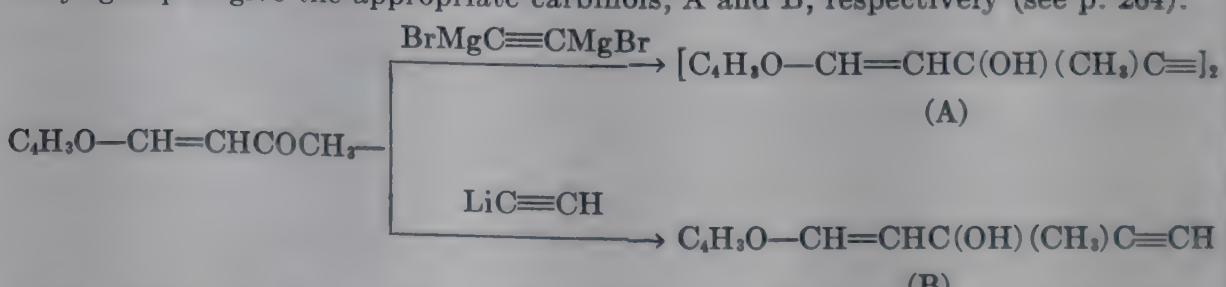
With diphenyl mercury, furfurylideneacetone undergoes resinification with simultaneous deposition of mercury.[261]

Henecka[262] has prepared 5-phenyl-5-cyano-4-(2-furyl)pentan-2-one, XXI, [b.p. 168° (0.8 mm.)] by condensing furfurylideneacetone with phenylacetonitrile. Subsequent hydrogenation gives the cyclization product, 2-methyl-4-(2-furyl)-5-phenylpiperidine, XXII, b.p 138–140° (1.2 mm.).



XXI XXII

ammonia,[260] reaction with furfurylideneacetone goes forward by attack on the carbonyl group to give the appropriate carbinols, A and B, respectively (see p. 264).



[259] Yasnopol'skii, *Zhur. Obshchei Khim., J. Gen. Chem.*, **19**, 300 (1949); *C. A.*, **43**, 6573 (1949).

[260] Oroshnik and Mebane, *J. Am. Chem. Soc.*, **71**, 2062 (1949).

[261] Koton and Zorina, *Zhur. Obshchei Khim. J. Gen. Chem.*, **19**, 1137 (1949); *C. A.*, **44**, 2943 (1950).

[262] Henecka, *Chem. Ber.*, **82**, 104 (1950).

Aliphatic nitro compounds react with furfurylideneacetone and furfurylideneacetophenone under the influence of sodium methoxide[225] or secondary amines[263] to give γ-nitro-β-(2-furyl)alkanone types, XXIII, several of which are listed below.

$$C_4H_3O{-}CH{=}CHCOR + R'R''CHNO_2 \rightarrow C_4H_3O{-}CHCH_2COR$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R'R''CNO_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{XXIII}$$

Compound XXIII

R	R′	R″	Physical constants (°C.)
CH_3	C_2H_5	H	b.p. 116–117 (1 mm.); d_{20}^{20} 1.1414; n_D^{20} 1.4859
CH_3	CH_3	CH_3	b.p. 114–115 (1 mm.); d_{20}^{20} 1.1558; n_D^{20} 1.4905
C_6H_5	H	H	m.p. 49.5–50
C_6H_5	C_2H_5	H	m.p. 81–82
C_6H_5	CH_3	CH_3	m.p. 82–82.5
C_6H_5	C_6H_5	H	m.p. 153–153.5
p-C_6H_4Br	H	H	m.p. 72–73
p-C_6H_4Br	C_6H_5	H	m.p. 87–88.5

With *p*-thiocresol, in the presence of piperidine, furfurylideneacetophenone gives rise to β-(2-furyl)-β-(*p*-methylthiophenoxy)propiophenone, $C_4H_3O{-}CH(SC_6H_4CH_3)CH_2COC_6H_5$, m.p. 78.5°; *p*-toluenesulfinic acid adds similarly.[264]

Alkali bisulfites add to furfurylideneacetone and its homologs, giving rise to saturated β-ketosulfonic acids[202, 265] which may be resinified for use as ion-exchangers.[196] In the presence of sodium alkoxides, dialkyl phosphites add similarly with formation of β-ketophosphonic esters, XXIV.[266]

$$C_4H_3O{-}CH{=}CHCOCH_3 \xrightarrow[RONa]{(RO)_2POH} C_4H_3O{-}CHCH_2COCH_3$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad PO(OR)_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \text{XXIV}$$

R	b.p. (°C.)	n_D^{20}	d_4^{20}
CH_3	163–164 (6 mm.)	1.4835	1.2181
C_2H_5	192–193 (16 mm.)	1.4755	1.1616
C_4H_9	182 (4 mm.)	1.4730	1.0995
i-C_4H_9	161 (3 mm.)	1.4711	1.0932

Interestingly enough, however, the related 3-(2-furyl)acrolein adds this reagent to the carbonyl group rather than to the olefinic side chain.[266]

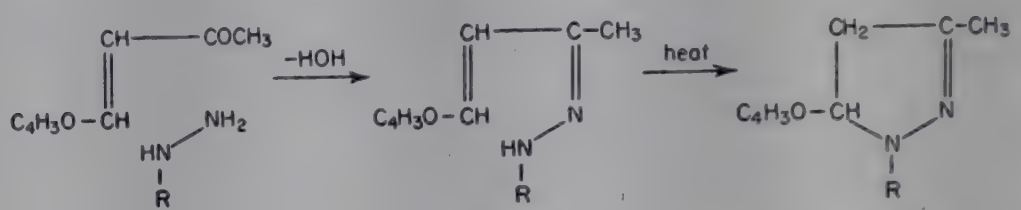
[263] Kloetzel, *J. Am. Chem. Soc.*, **69**, 2271 (1947).

[264] Gilman and Dickey, *Iowa State Coll. J. Sci.*, **6**, 381 (1932).

[265] Thurston (to American Cyanamid Co.), U. S. Pat. 2,385,314 (1945); *C. A.*, **40**, 609 (1946).

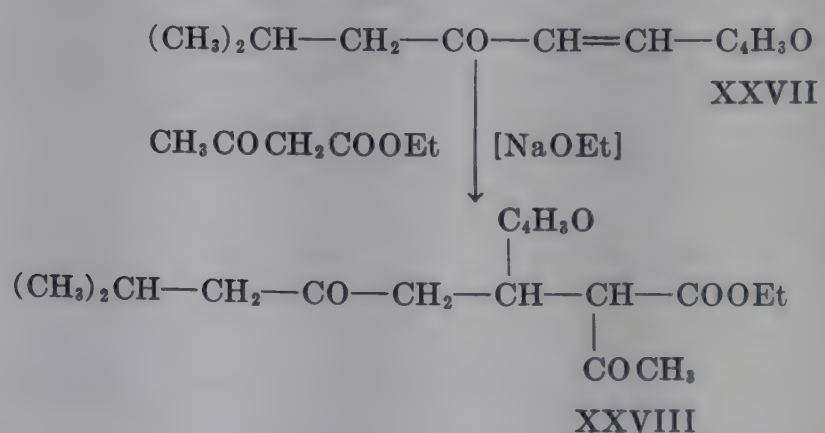
[266] Pudovik, *Doklady Akad. Nauk. S. S. S. R.*, **73**, 499 (1950); *C. A.*, **45**, 2856 (1951).

Reaction of the furylalkenones with the common carbonyl reagents has, in many instances, failed to produce the anticipated derivative, no doubt as a result of secondary reactions involving the olefinic linkage. Thus, difurfurylideneacetone and hydroxylamine give a product, m.p. 162–164°, which Minunni[200] formulated as an hydroxylamine addition compound of the oxime. The phenylhydrazone, XXV (R = C_6H_5), of furfurylideneacetone readily undergoes internal addition to form 1-phenyl-3-methyl-5-furylpyrazoline, XXVI (R = C_6H_5), m.p. 102–103°[185] (see also [214, 256]). In the same way, 3-methyl-5-furylpyrazoline, XXVI (R = H), [b.p. 127–128° (22 mm.); d_4^{20} 1.1507] is formed from the hydrazone.[267]



XXV XXVI

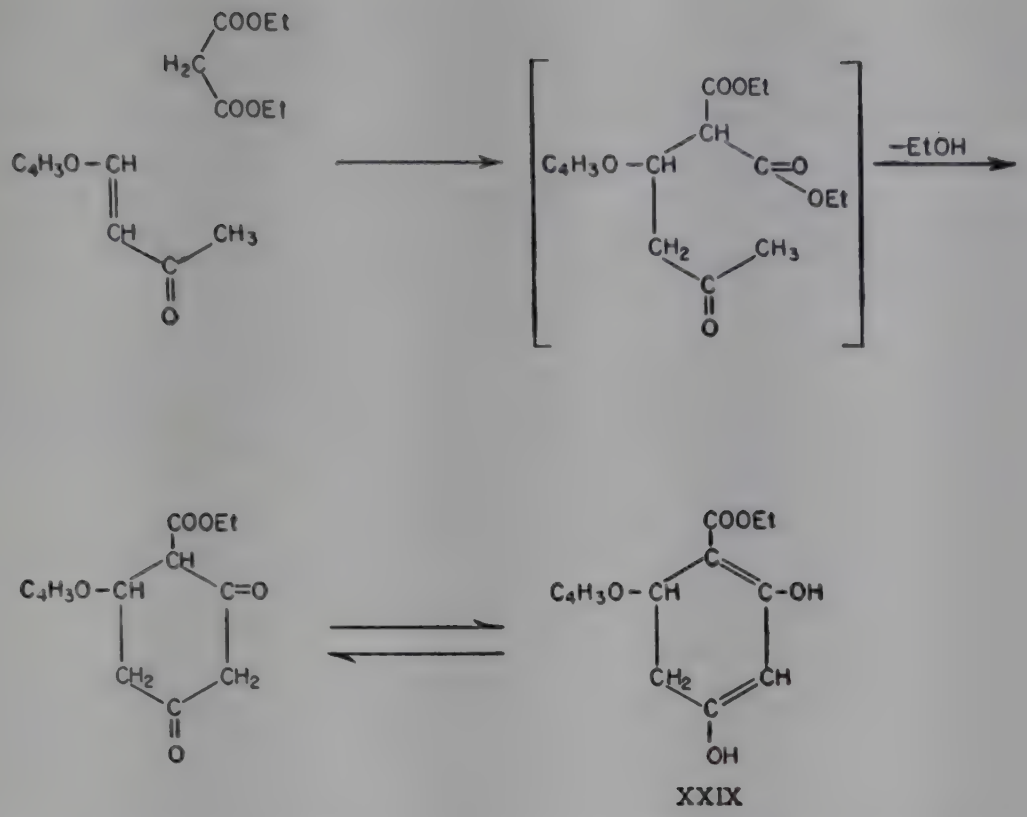
Sodioacetoacetic ester adds across the lateral double bond of 1-furyl-5-methyl-1-hexene-3-one, XXVII (derived from furfural and methyl *i*-butyl ketone) to give 2-acetyl-3-furyl-5-oxo-7-methyloctanoic ester, XXVIII (Et ester, m.p. 116°; Bu ester, m.p. 98°).[197]



XXVIII

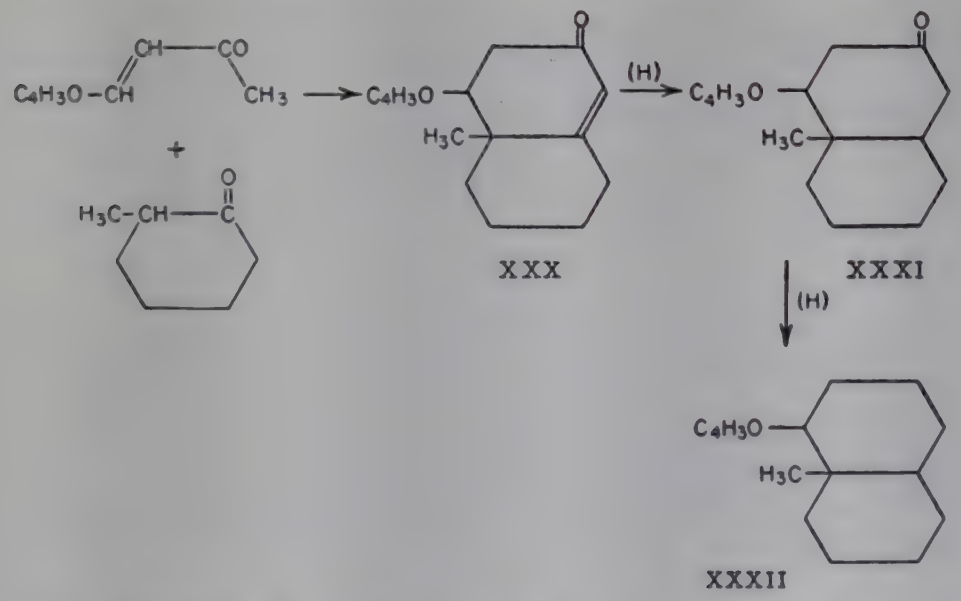
Sodiomalonic ester reacts normally with furfurylideneacetone, but under the conditions employed by Vorländer,[268] the primary addition product cyclizes to form 5-furyl-4-carbethoxy-5,6-dihydroresorcinol, XXIX, m.p. 102°. Hydrolysis and decarboxylation of XXIX gives rise to furyldihydroresorcinol, m.p. 150° (dec.), which is cleaved by alkali hypochlorites to β-(2-furyl)glutaric acid (p. 612). Related to this condensation-addition

[267] Kizhner, *J. Russ. Phys. Chem. Soc.*, **61**, 781 (1929); *C. A.*, **23**, 4698 (1929).
[268] Vorländer, *Ann.*, **294**, 273 (1897).



XXIX

reaction is the work of King and Robinson[269] on the synthesis of polynuclear products related to the sterols. These investigators reacted furfuryl-ideneacetone with the sodium derivatives of 2-methylcyclohexanone and related types. In the former instance they obtained 2-oxo-4-(2-furyl)-10-methyl-$\Delta^{1,9}$-octalin, XXX, which was reduced stepwise to the decalin derivatives, XXXI and XXXII. Compounds related to flavanone, 2-(2-furyl)-

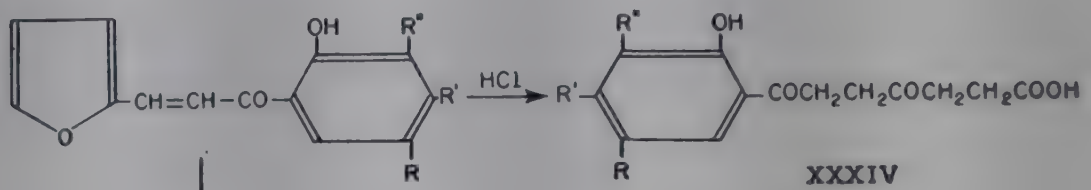


XXX XXXI XXXII

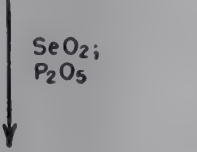
chromanone (XXXIII; R = H) and its 7-methoxy derivative, have been

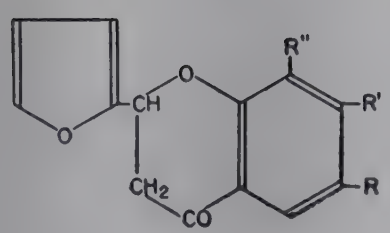
[269] King and Robinson, *J. Chem. Soc.*, **1941**, 465.

synthesized by cyclization of furfurylidene-*o*-hydroxyacetophenones on heating in the presence of selenium dioxide,[234] or phosphorus pentoxide.[227] The use of boiling, alcoholic mineral acid as the cyclization medium, which is successful in the preparation of flavanone from benzylidene-*o*-hydroxyacetophenone, fails here due to hydrolytic fission of the furan nucleus and formation of δ-(*o*-hydroxyphenacyl)levulinic acids, XXXIV[230, 234] (see also Chapter 14).



XXXIV



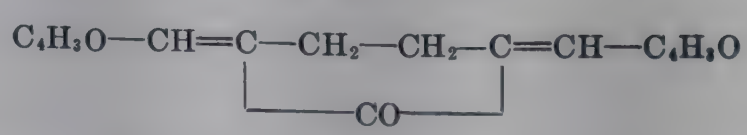


XXXIII

Alicyclic Ketones

Furan Derivatives of Cyclopentanone.

2,5-Difurfurylidenecyclopentanone: (pyroxanthin);

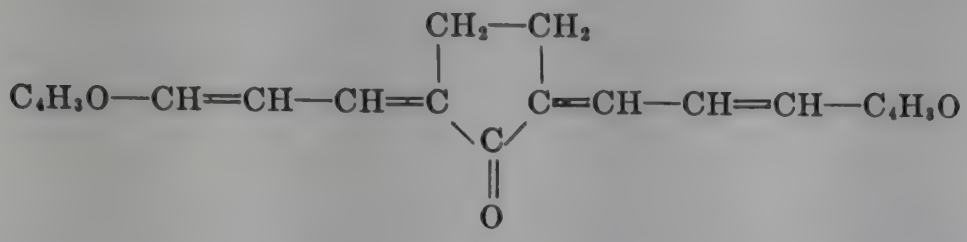


yellow-orange crystalline solid, m.p. 162, 163°; by condensation of furfural (2 moles) with cyclopentanone (1 mole),[270] and from crude wood distillate following treatment with caustic alkali.[271] It dissolves in concentrated H_2SO_4 with an intense blue-violet color, and forms salts with dry hydrogen chloride.[243] With bromine in carbon disulfide, a dibromotetrabromide is obtained from which, by the action of zinc, is derived a dibromo compound (m.p. 180°, dec.), presumably the bis(5-bromofurfurylidene)cyclopentanone.[270] For catalytic hydrogenation, see Alexander *et al.*[81]

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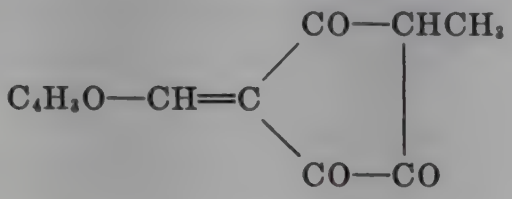
[270] Vorländer and Hobohm, *Ber.*, **29**, 1836 (1896).
[271] Hill, *Ber.*, **10**, 936 (1877).

2,5-Bis(3-furylallylidene)cyclopentanone:



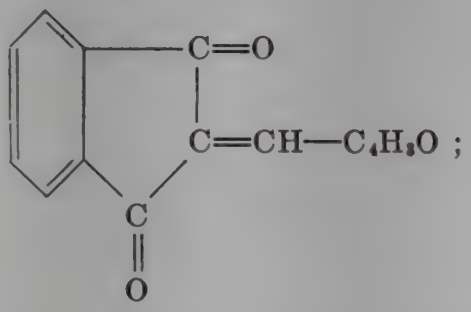
bright yellow needles, m.p. 149°; in 90 per cent yield from furylacrolein and cyclopentanone in alcoholic sodium hydroxide at 0–10°.[174]

5-Furfurylidene-3-methyl-1,2,4-cyclopentanetrione:



red-yellow prisms, m.p. 199° (dec.); in 58 per cent yield by reaction of furfural with methylcyclopentanetrione in aqueous sodium hydroxide.[272]

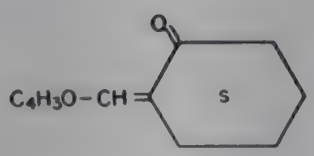
2-Furfurylidene-1,3-dioxohydrindene:



greenish needles from pyridine-alcohol, m.p. 203°; by heating furfural with 1,3-dioxohydrindene.[273]

Furan Derivatives of Cyclohexanone.

2-Furfurylidenecyclohexanone:

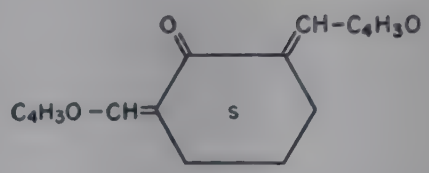


yellow crystals, m.p. 47°; by condensing furfural and cyclohexanone in ether with sodium amide.[274] Reduced to 2-furfurylcyclohexanone, b.p. 136° (17 mm.) by the action of sodium amalgam in alcohol.[274]

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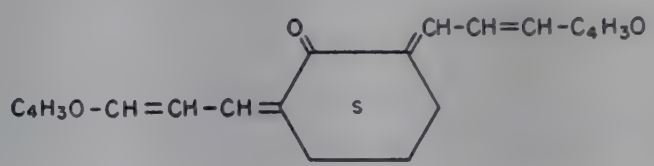
[272] Diels and Bocking, *Ber.*, **42**, 1576 (1909).
[273] Kostanecki and Laczkowski, *Ber.*, **30**, 2138 (1897).
[274] Wolff, *Ann. chim.* (*9*), **20**, 82 (1923).

2,6-Difurfurylidenecyclohexanone:



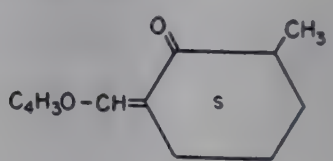
bright yellow needles, m.p. 143°, 145.5–146°. Obtained as in the preceding preparation using either sodium alkoxide or sodium amide as the condensing agent[274, 275] (see also [276]). Reduction with sodium amalgam gives 2,6-difurfurylcyclohexanone, m.p. 53°, in low yield.[274] Addition of alkali bisulfites proceeds as expected, saturating the olefinic double bonds with formation of the bis-sulfonic acid.[196, 202] With concentrated sulfuric acid, difurfurylidenecyclohexanone gives an intense violet color; with diluted sulfuric acid, fuchsin-red.[275] For catalytic hydrogenation, see [81].

2,6-Bis(3-furylallylidene)cyclohexanone:

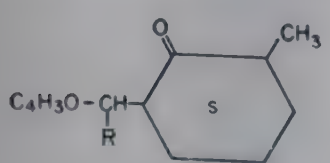


yellow crystals, m.p. 166°; in 93 per cent yield from furylacrolein and cyclohexanone in alcoholic sodium hydroxide.[174]

6-Furfurylidene-2-methylcyclohexanone:

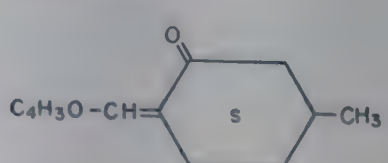


m.p. 53°; from furfural and 2-methylcyclohexanone in ether with sodium amide.[174] Sodium amalgam reduction gave 6-furfuryl-2-methylcyclohexanone, b.p. 146° (16 mm.). Addition of the Grignard reagent proceeded as expected to give the products indicated below:



when R = $C_6H_5CH_2$, b.p. 213° (14 mm.)
= C_6H_5 b.p. 206° (17 mm.)
= p—CH_3—C_6H_4 b.p. 220° (16 mm.)

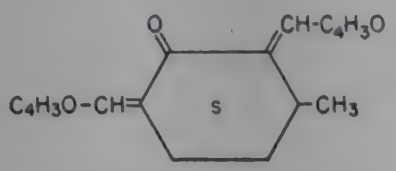
6-Furfurylidene-3-methylcyclohexanone:



[275] Boedtker, *J. pharm. chim.*, **6**, 204 (1927); *C. A.*, **22**, 585 (1928).
[276] Kursanov and Solodkov, *Compt. rend. acad. sci. U. R. S. S.*, **27**, 797 (1940); *C. A.*, **35**, 1770 (1941).

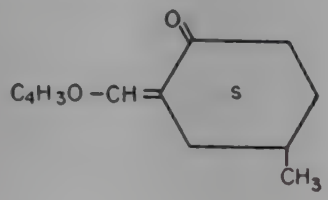
m.p. 43°; $[\alpha]_D$ − 12°; from furfural and 3-methylcyclohexanone with sodium methoxide.[274] 6-Furfuryl-3-methylcyclohexanone, b.p. 142–143° (17 mm.); $[\alpha]_D$ −5°; by reduction of the furfurylidene compound with sodium amalgam.[274]

2,6-Difurfurylidene-3-methylcyclohexanone:



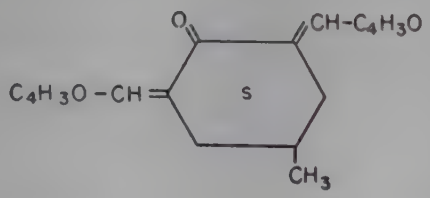
m.p. 68°; $[\alpha]_D$ −172°; obtained as in preceding preparation using 2 moles of furfural per mole of 3-methylcyclohexanone.[174] Sodium amalgam reduction gave 2,6-difurfuryl-3-methylcyclohexanone, b.p. 196–200° (16 mm.); $[\alpha]_D$ −7°.[174]

6-Furfurylidene-4-methylcyclohexanone:



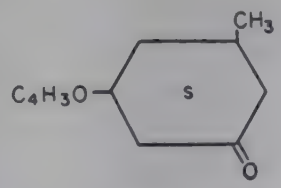
m.p. 42°; from furfural and 4-methylcyclohexanone and furfural with sodium amide.[174] Reduction produced 6-furfuryl-4-methylcyclohexanone, b.p. 148–150° (20 mm.).[174]

2,6-Difurfurylidene-4-methylcyclohexanone:



m.p. 94°; as in the preceding preparation.[174] 2,6-Difurfuryl-4-methylcyclohexanone, m.p. 52°, obtained on reduction as before.[174]

3-Methyl-5-(2-furyl)cyclohexanone:



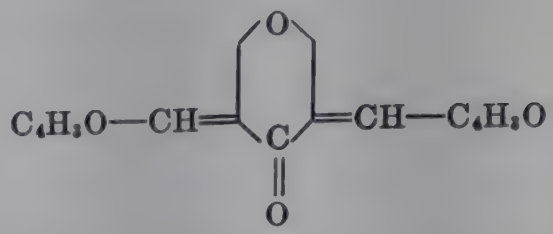
b.p. 147–148° (12 mm.); d_4^{20} 1.0619; n_D^{20} 1.4998; **semicarbazone,** m.p. 172–173°. Obtained[277] by reduction of the correspondingly substituted 2-cyclohexenone derived from furfurylidenebis(acetoacetic ester) (see p. 613). Substituted spirohydantoins are obtained by treatment with potassium cyanide and ammonium carbonate in aqueous alcoholic solution.[277]

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[277] Henze, Wilson and Townley, *J. Am. Chem. Soc.*, **65**, 963 (1943).
[278] Cornubert, Delmas, Monteil and Viriot, *Bull. soc. chim. France*, **1950**, 36.
[279] Peak, Robinson and Walker, *J. Chem. Soc.*, **1936**, 752.

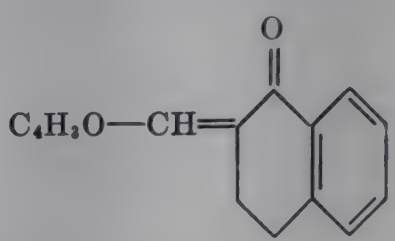
C. Related Products.

Difurfurylidenetetrahydro-4-pyranone:



m.p. 180.5–181°; from furfural and tetrahydropyranone in alcohol using a basic condensing agent[278] (see also Chapter 15).

Furfurylidene-α-tetralone: [2-furfurylidene-3,4-dihydro-1(2*H*)-naphthalenone];



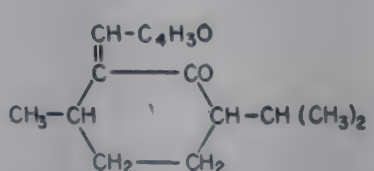
m.p. 75–76°; by condensation of furfural with α-tetralone in aqueous-alcoholic sodium hydroxide. The **6-methoxy derivative,** m.p. 104.5°, was prepared similarly. Condensation of these products with acetoacetic ester in the presence of sodium ethoxide gives rise to ethyl 1-furyl-3-oxo-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate (α-form, m.p. 119–120°; β-form, m.p. 120–121°) and the corresponding 7-methoxy derivative (m.p. 122°), respectively.[279]

Furfurylidene-1-oxo-1,2,3,4-tetrahydrophenanthrene: [2-furfurylidene-3,4-dihydro-1(2*H*)-phenanthrenone];



m.p. 119–120°[226] (see also Chapter 14).

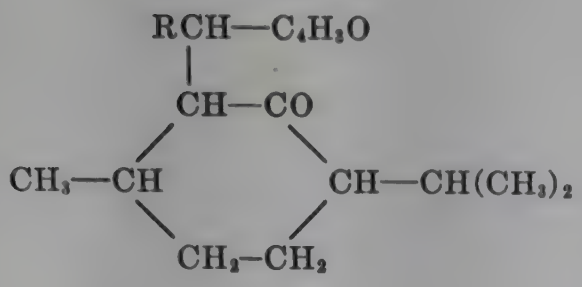
Furfurylidenementhone:



n_D^{15} 1.5649; $[\alpha]_D^{15}$ 190°51′; a thick, yellow liquid which turns brown on exposure to air. Obtained by condensing furfural with menthone, $[\alpha]_D^{17}$ 3°20′, by means of sodium ethoxide. Product was transformed into a series of alkylfurylmenthomethanes, I, by the action of appropriate Grignard reagents.[280]

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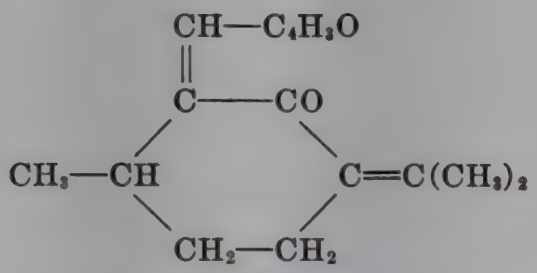
[280] Boedtker, Wiger and Aagaard, *J. pharm. chim.*, **6**, 193 (1927); *C. A.*, **22**, 584 (1928).



I

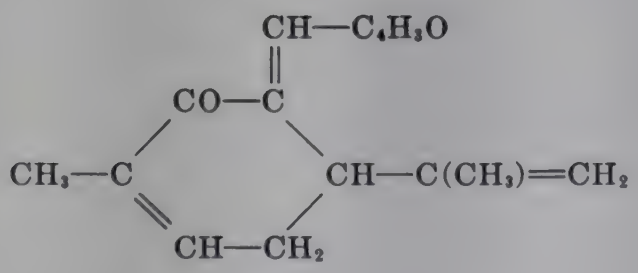
when R = CH_3, b.p. 149–150° (9 mm.); n_D^{15} 1.4986; $[\alpha]_D^{15}$ −19°7′.
R = C_2H_5, b.p. 165° (12 mm.); n_D^{15} 1.4941; optically inactive.
R = *n*—C_3H_7, b.p. 164° (9 mm.); n_D^{15} 1.4929; optically inactive.
R = *i*—C_3H_7, b.p. 162° (9 mm.); n_D^{15} 1.4938; $[\alpha]_D^{15}$ 49°58′ (in C_6H_6).
R = *n*—C_4H_9, b.p. 174° (10 mm.); n_D^{15} 1.4905; $[\alpha]_D^{15}$ 13°22′ (in C_6H_6).
R = *i*—C_4H_9, b.p. 169–170° (10 mm.); n_D^{15} 1.4911; $[\alpha]_D^{15}$ 19°33′ (in C_6H_6).
R = $CH_2CH_2CH(Me)_2$; b.p. 181° (10 mm.) n_D^{15} 1.4915; $[\alpha]_D^{15}$ 21°46′.
R = C_6H_5, b.p. 218° (10 mm.), resinous; m.p. 93.5–94°; n_D^{19} 1.5415; $[\alpha]_D^{18.5}$ 22°45′ (in C_6H_6).

Furfurylidenepulegone:



b.p. 168–170° (0.25 mm.).[281] For reaction with the Grignard reagent, see Maxim *et al.*[282]

Furfurylidenecarvone:

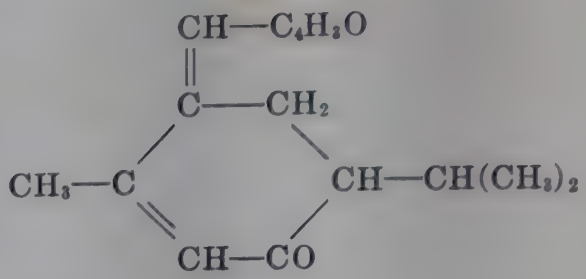


b.p. 188–190° (15 mm.).[283]

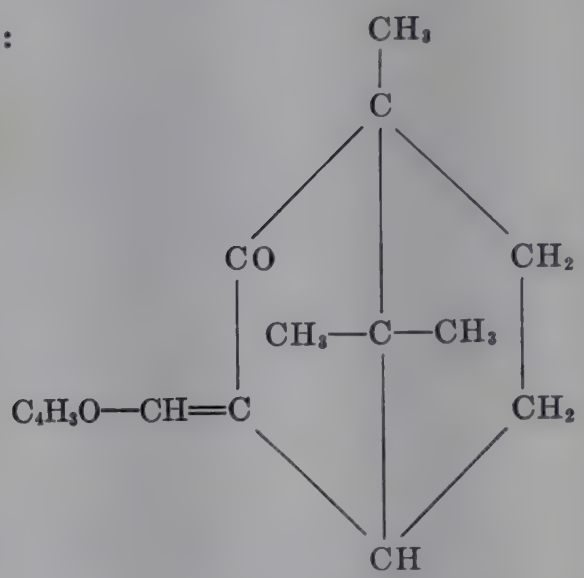
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[281] Thoms and Soltner, *Arch. Pharm.*, **268**, 157 (1930); *C. A.*, **24**, 3235 (1930).
[282] Maxim, Zugravescu and Teodorescu, *Bull. soc. chim.*, **7**, 382 (1940).
[283] Maxim, Zugravescu and Teodorescu, *Bul. Chim. Soc. Chim. Romania* (*2*), **3A**, 24 (1941–1942); *C. A.*, **38**, 5496 (1944).

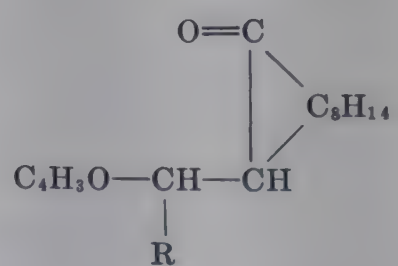
Furfurylidenepiperitone: m.p. 66°.[283a]



Furfurylidenecamphor:



m.p. 64°; $[\alpha]_D$ 339°; in 20 per cent yield from furfural and camphor in benzene using sodium amide as the condensing agent.[274] Weaker bases (caustic alkalies, sodium alkoxides) fail to bring about the reaction.[148] Reduction with sodium amalgam in alcohol produces furfurylcamphor, m.p. 65°; $[\alpha]_D$ + 108°. Catalytic hydrogenation (Raney Ni) gives rise to tetrahydrofurfurylcamphor, b.p. 160° (14 mm.); $d_4^{23.6}$ 1.0303; n_D^{24} 1.49543; $[\alpha]_D$ + 42°. Organomagnesium halides add to the olefinic linkage, subsequent hydrolysis yielding the appropriately substituted furylcamphomethanes (II) as indicated below:

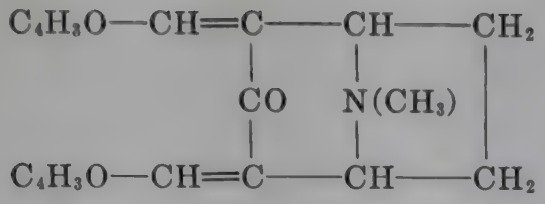


II

when R =	$C_6H_5CH_2$	b.p. 222° (14 mm.); $[\alpha]_D$ + 57°
=	C_6H_5	m.p. 114°; $[\alpha]_D$ + 66°
=	p—CH_3—C_6H_4	b.p. 234° (17 mm.); $[\alpha]_D$ + 59°
=	p—CH_3O—C_6H_4	b.p. 255° (17 mm.); $[\alpha]_D$ + 66°

[283a] Dewar, Morrison and Read, *J. Chem. Soc.*, **1936**, 1598.

Difurfurylidenetropinone:



m.p. 138°; from furfural and tropinone under the influence of sodium ethoxide. **Hydrochloride,** m.p. 237–238°. **Methiodide,** m.p. 281° (dec.). The compound shows great similarity in behavior to difurfurylideneacetone and difurfurylidenecyclopentanone. It acts as a dye, coloring wool greenish-yellow.[284]

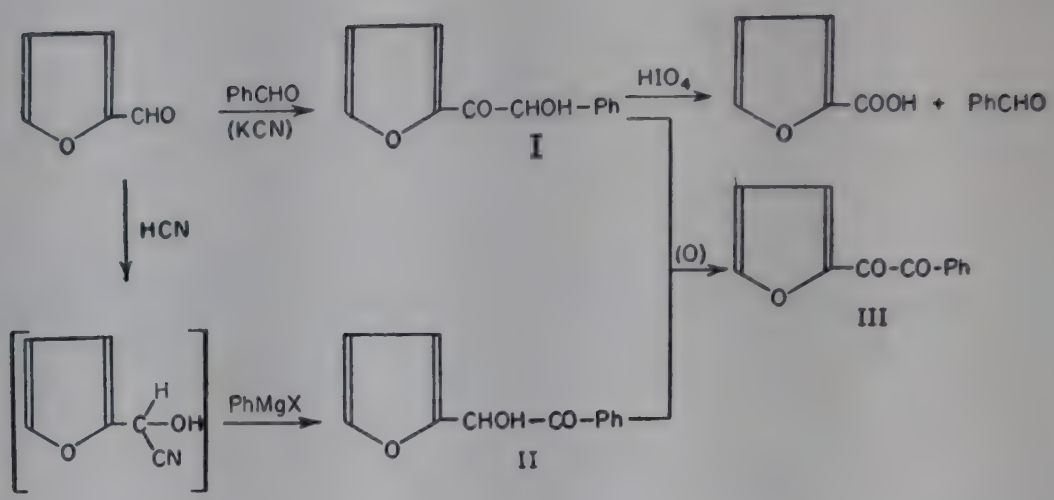
Furoin, Furil and Related Types

Preparation of furoin from furfural by the well known acyloin condensation is much less satisfactory from the standpoint of yield than is the analogous synthesis of benzoin from benzaldehyde. This is explainable in terms of the tarry by-products which invariably accompany the formation of furoin by this procedure. Unfortunately, however, the nature of the side reaction(s) responsible for these tars remains obscure, and it has not been possible to find experimental conditions which materially curtail their occurrence. Accordingly, while some improvement[285] has been observed since Fischer[286, 287] first reported the isolation of furoin in 1880, the yield (*ca.* 40 per cent) still leaves much to be desired.

Several mixed acyloins containing a furan nucleus are also known (see below). For example, condensation of a mixture of furfural and benzaldehyde in the presence of potassium cyanide gives rise to furobenzoin,[d] I, in admixture with furoin and benzoin. Fischer[287] recognized the possibility that this product, one of the earliest known mixed benzoins, might be I or the isomeric benzfuroin, II, or a mixture of both. On the basis of the behavior of the oximes (α and β) in the Beckmann transformation, Werner and Detscheff[288] assigned configuration I, the correctness of which is supported by the isolation of benzaldehyde and furoic acid as the products of oxidation with periodic acid,[289] and by the independent synthesis of II by another procedure.[290] Under mild oxidizing conditions, I and II are converted to the same benzfuril, III.

[d] In naming the mixed acyloins, we have adopted the nomenclature proposed by Buck and Ide.[291] In this system, the syllable "-oin" is placed after the aldehyde whose —CHO group becomes —CHOH.

[284] Willstätter, *Ber.*, **30**, 2679 (1897).
[285] Hartman and Dickey, *J. Am. Chem. Soc.*, **55**, 1228 (1933).
[286] Fischer, *Ber.*, **13**, 1334 (1880).
[287] Fischer, *Ann.*, **211**, 214 (1882).
[288] Werner and Detscheff, *Ber.*, **38**, 69 (1905).
[289] Clutterbuck and Reuter, *J. Chem. Soc.*, **1935**, 1467.
[290] Asahina and Teresaka, *J. Pharm. Soc. Japan*, **494**, 19 (1933); *Chem. Centr.*, **1923, III**, 434.

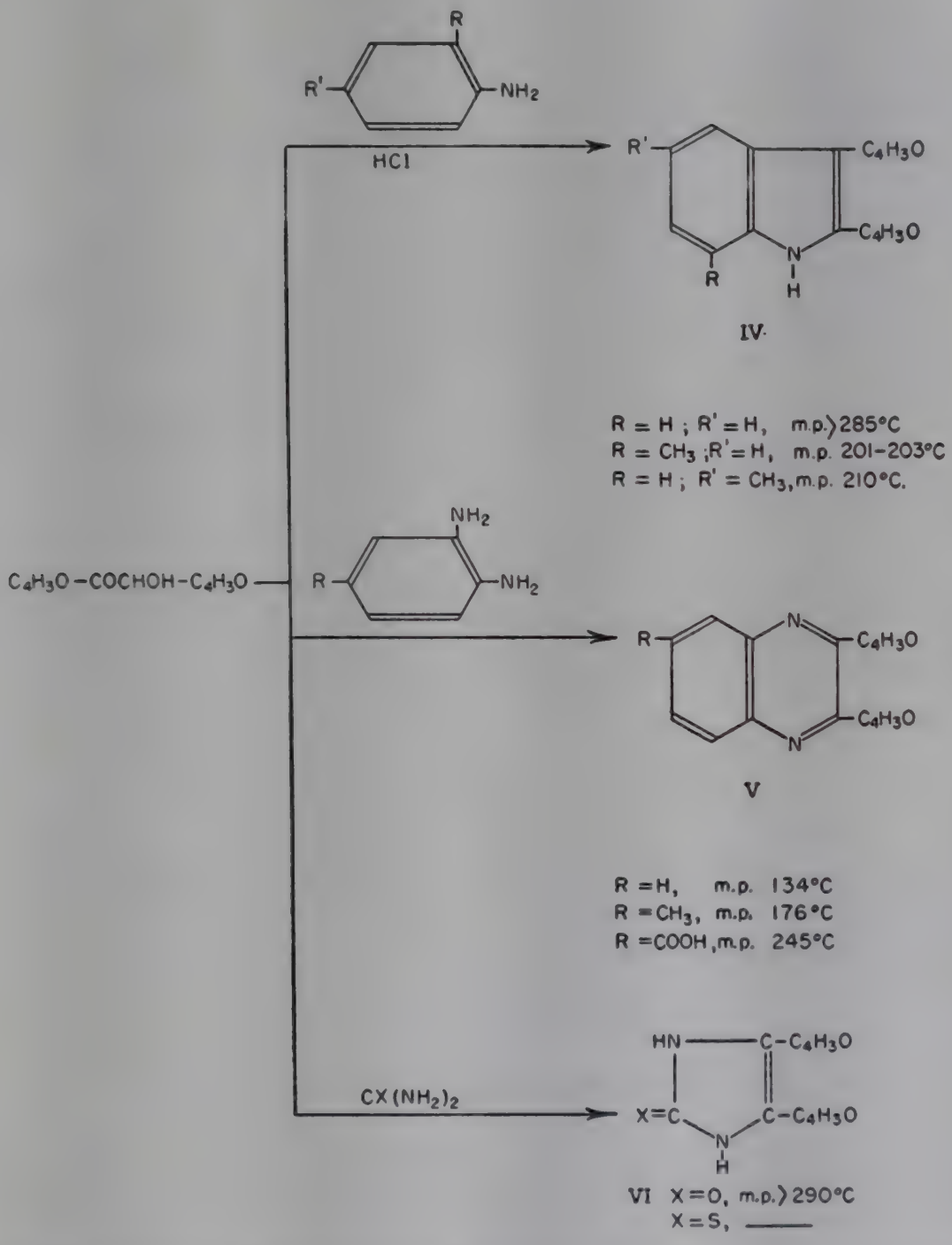


Furoin: (furoylfurylcarbinol); $C_4H_3O—CO—CHOH—C_4H_3O$; m.p. 135°. By self-condensation of furfural in the presence of potassium cyanide.[287, 292, 285, 293] For thermochemical data, see Barker[294] and Landrieu.[295] Oxidation to furil is discussed later. For electrolytic oxidation, see Law.[296] For comparative rates of autoxidation of furoin, furobenzoin, benzfuroin and benzoin, see Weissberger *et al.*[297] For the use of furoin as a reducing agent in the transformation of aromatic nitro compounds to azoxy compounds, see Nisbet.[298] For attempted methylation, see Irvine and McNicoll.[299] Reduction by the action of fermenting yeast produces hydrofuroin, $C_4H_3O—CHOH—CHOH—C_4H_3O$[300] (see p. 383). Catalytic (Raney Ni) hydrogenation gives the saturated glycol, 1,2-bistetrahydrofuryl-1,2-ethanediol, which is oxidized quantitatively to tetrahydrofurfural by lead tetracetate.[301] With tin and hydrochloric acid, furoin is converted into desoxyfuroin, $C_4H_3O—CO—CH_2—C_4H_3O$[82] (see also [84, 287]).

Esterification with acetic anhydride gives **acetylfuroin,** m.p. 76–77°.[287] **Benzoylfuroin,** m.p. 92–93°.[302] For attempted alkylation of furoin to obtain the corresponding α-keto ethers, see Irvine and McNicoll.[299] On refluxing furoin with a mixture of aniline and aniline hydrochloride, there is obtained 2,3-difurylindole (IV, R and R′ = H).[303] The corresponding methylindoles are obtained by using *o*- and *p*-toluidine in place of aniline,

[291] Buck and Ide, *J. Am. Chem. Soc.*, **52**, 220 (1930).
[292] Corson and McAllister, *J. Am. Chem. Soc.*, **51**, 2822 (1929).
[293] Lespagnol and van Thienen, *Bull. sci. pharmacol.*, **45**, 49 (1938).
[294] Barker, *J. Phys. Chem.*, **29**, 1345 (1925).
[295] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).
[296] Law, *J. Chem. Soc.*, **89**, 1437 (1906).
[297] Weissberger, Strasser, Mainz, and Schwarze, *Ann.*, **478**, 112 (1930).
[298] Nisbet, *J. Chem. Soc.*, **1928**, 3121.
[299] Irvine and McNicoll, *J. Chem. Soc.*, **93**, 1601 (1908).
[300] Neuberg, Lustig and Cagan, *Arch. Biochem.*, **1**, 391 (1943).
[301] Wilson, *J. Chem. Soc.*, **1945**, 52.
[302] Green, *J. Chem. Soc.*, **1926**, 328.
[303] Sircar and Guha, *J. Indian Chem. Soc.*, **13**, 704 (1936); *C. A.*, **31**, 3911 (1937).

and with naphthylamines, difurylbenzindoles are formed.[303] Condensation of furoin with *o*-phenylenediamines[304] proceeds with elimination of water and hydrogen to form difurylquinoxalines, V, which have also been derived from furil and the *o*-diamines.[305, 306] With urea, furoin gives rise to difuryliminazolone, VI (X = O); with thiourea, the sulfur analog (VI, X = S).[303]



[304] Fischer, *Ber.*, **25**, 2826 (1892).
[305] Zehra, *Ber.*, **23**, 3625 (1890).
[306] Mamalis and Petrow, *J. Chem. Soc.*, **1950**, 703.
[307] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany, 1930.

Furoin phenylhydrazone: m.p. 79–81°[84]; **semicarbazone,** m.p. 125°[307]; **α-oxime,** m.p. 160–161° (acetyl derivative, m.p. 113°; carbanilide, m.p. 56°); **β-oxime,** m.p. 102° (acetyl derivative, m.p. 108°; carbanilide, m.p. 120°).[288] For study of Beckmann rearrangement of the oximes, see Werner and Detscheff.[288] For copper salts of the oximes of furoin and of furobenzoin, see Feigl *et al.*[308] Reduction of furoin oxime using zinc and caustic alkali gives difuryl-2-amino-1-ethanol,

$$C_4H_3O—CH(NH_2)—CHOH—C_4H_3O^{293}$$

(see p. 270).

Furobenzoin: (furoylphenylcarbinol); $C_4H_3O—CO—CHOH—C_6H_5$; m.p. 137–139°, 139–141°; prepared by heating a mixture of furfural and benzaldehyde with potassium cyanide in aqueous alcohol.[287, 309, 293] Also formed in low yield by slow addition of sodium ethoxide to a cold, alcoholic solution of furfural and benzoylmandelonitrile.[302] Behavior is similar to that of furoin.

Furobenzoin oxime: α-form, m.p. 160° (acetyl derivative, m.p. 115°; carbanilide, non-cryst.); β-form, m.p. 90° (acetyl derivative, m.p. 96°; carbanilide, m.p. 138°).[288] With benzenesulfonyl chloride, the α-oxime rearranges and breaks down to form furonitrile and benzaldehyde.[288] Reduction of the oxime gives rise to furylphenylethanolamine, $C_4H_3O—CH(NH_2)—CHOH—C_6H_5$[293] (see p. 271).

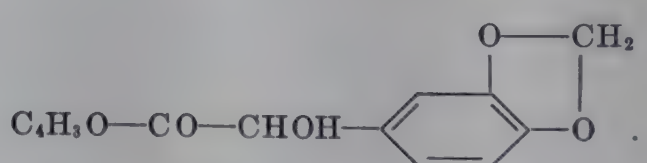
Benzfuroin: (furylbenzoylcarbinol): $C_4H_3O—CHOH—CO—C_6H_5$; m.p. 119°. This structural isomer of furobenzoin (above) is derived from furfural cyanohydrin by the action of phenylmagnesium chloride[290] (see also [310, 311]).

Furo-*p*-dimethylaminobenzoin: (furoyl-*p*-dimethylaminophenylcarbinol);

$$C_4H_3O—CO—CHOH—C_6H_4[N(CH_3)_2]$$

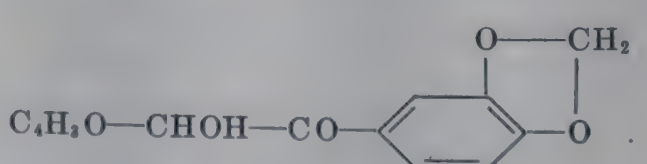
m.p. 168°; by condensation of furfural and *p*-dimethylaminobenzaldehyde in aqueous alcohol in the presence of potassium cyanide.[291, 310]

Furopiperoin: (furoylpiperonylcarbinol);



Obtained as the **benzoic ester,** m.p. 140–141°, by condensation of piperonal with benzoylfurfural cyanohydrin in alcohol by means of sodium ethoxide.[302]

Piperfuroin: (furylpiperonoylcarbinol);



Isomeric with preceding product. Obtained, as **benzoic ester,** m.p. 132.5–133.5°, from furfural and benzoylmethylenedioxymandelonitrile in alcohol by the addition of sodium ethoxide.[302]

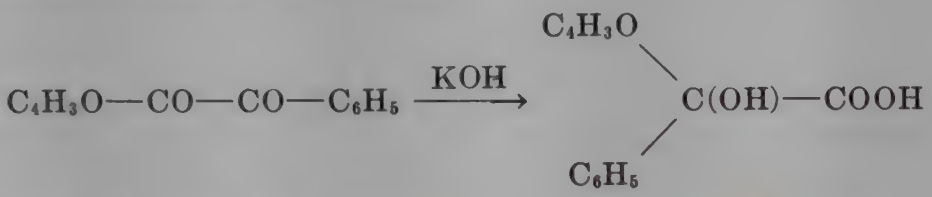
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[308] Feigl, Sicher and Singer, *Ber.*, **58,** 2294 (1925).
[309] Tiffeneau and Levy, *Bull. soc. chim.*, **49,** 725 (1931)
[310] Buck and Ide, *J. Am. Chem. Soc.*, **53,** 2350 (1931).
[311] Buck and Ide, *J. Am. Chem. Soc.*, **53,** 2784 (1931)

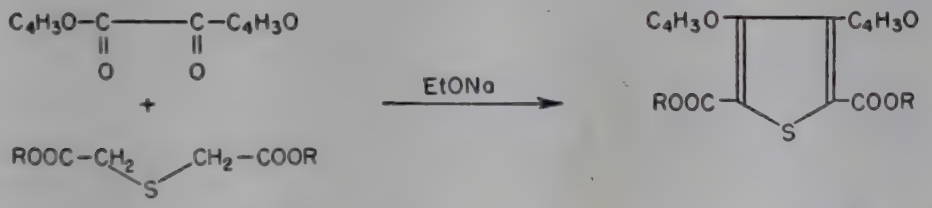
Furoin dissolves in dilute alcoholic alkali giving highly-colored solutions from which furil may be obtained in high yield by oxidation with air[287] or iodine.[292] The oxidation is also conveniently achieved by heating furoin in aqueous pyridine with copper sulfate[285]; by blowing air through furoin in acetic acid using cobalt acetate or copper benzoate as a catalyst[312]; by using ammonium nitrate in glacial acetic acid, with[313] and without[314] a catalyst.

Furil is split into ethyl furoate and furfural on standing in alcoholic potassium cyanide.[315] Treatment with nitromethane and sodium ethoxide brings about similar cleavage, but the liberated furfural condenses with the nitroparaffin to give, in low yield, 2-(2-nitrovinyl)furan.[316]

In strongly alkaline solution, furil is converted into a very unstable product which Fischer[287] (see also [317]) was unable to obtain in the pure state. He suggested it was furilic acid by analogy with the benzilic acid transformation, and was successful, by similar treatment of benzfuril, in isolating benzfurilic acid, m.p. 108°.



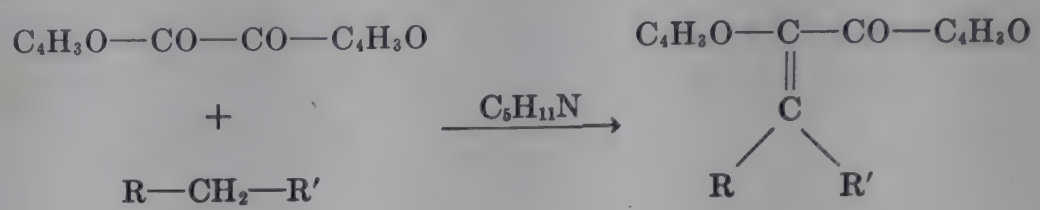
Condensation of furil with thiodiglycolic ester, using sodium ethoxide, produces 3,4-di(2-furyl)-2,5-thiophenedicarboxylic acid, m.p. 295° (dec.); dimethyl ester, m.p. 128–128.5°, which on decarboxylation gives rise to 3,4-di(2-furyl)thiophene, b.p. 172–173° (17 mm.).[318] It is interesting to



note that, using piperidine as the catalyst, condensation of furil with compounds possessing active methylene groups appears to involve only one of the carbonyl groups, whereas under similar conditions, both carbonyls of benzil enter into reaction. This observation is a result of the work of Sircar and Guha[303] who so condensed furil with acetoacetic ester, malonic

[312] Bremner, Jones and Imperial Chemical Industries Ltd., British Pat. 605,021 (1948); *C. A.*, **43**, 690 (1949).
[313] Weiss and Appel, *J. Am. Chem. Soc.*, **70**, 3666 (1948).
[314] Klein, *J. Am. Chem. Soc.*, **63**, 1474 (1941).
[315] Jourdan, *Ber.*, **16**, 658 (1883).
[316] Fujise, Takeuchi, Kamioka and Tiba, *Ber.*, **68**, 1272 (1935).
[317] Evans and Dehn, *J. Am. Chem. Soc.*, **52**, 252 (1930).
[318] Backer and Stevens, *Rec. trav. chim.*, **59**, 899 (1940).

ester and phenylacetonitrile, among others, and invariably obtained the bimolecular product as indicated below:



R	R′	m.p. (°C.)
CH_3CO	CH_3CO	>258
CH_3CO	COOEt	>275
COOEt	COOEt	>258
COOEt	CN	>255
C_6H_5	CN	>275
C_6H_5CONH	COOEt	>265

Furil: (difurylglyoxal); $C_4H_3O—CO—CO—C_4H_3O$; m.p. 162°, 165–166°. Prepared from furoin as indicated above. Thermochemical data, see Barker[294] and Landrieu.[295] **Phenylhydrazone,** m.p. 82–83°[84]; **bisphenylhydrazone,** $(C_4H_3O)_2C_2(NNHC_6H_5)_2$, m.p. 184°[84]; **monoxime:** α-form, m.p. 106°; β-form, m.p. 97–98°[84]; the **dioxime,** α-form, m.p. 166–168°,[319] goes over to the β-form, m.p. 188–190° (dec.), on heating.[84] The following references are concerned with the use of α-furilidoxime in the analytical determination of nickel: Soule,[320] Feigl,[321, 322] and Duval[323]; of iron, see Griffing and Mellon.[324]

Like benzil, furil forms a potassium derivative.[325] With urea it forms a **diureide,** m.p. 295°; with thiourea, a **dithioureide,** m.p. >300°.[303] It condenses with aldehydes, in the presence of an excess of ammonium hydroxide, forming **iminazoles:** 2-*p*-hydroxyphenyl-4,5-difuryliminazole, m.p. 235–236°, from *p*-hydroxybenzaldehyde, and the corresponding 2-*m*-hydroxyphenyl (m.p. 265°) and 2-*p*-nitrophenyl (m.p. 175°) derivatives from the appropriate aldehydes.[303] Using dry ammonia and two molecular proportions of the aldehyde, furil condenses with *o*-hydroxybenzaldehyde to form 1,2-bis(*o*-hydroxyphenyl)-1,2-bisfuramidoethane, m.p. >307°; with furfural, to give 1,2-difuryl-1,2-bisfuramidoethane, m.p. >280°[303] (see also [326]). For the related reaction of furfural with benzil and ammonia, see the work of Japp and Hooker.[327] When added to bromine in the cold, furil forms an **octabromide** which loses bromine and hydrogen bromide on application of heat.[287] Reduction of furil by fermenting yeast

[319] Reed, Banks and Diehl, *J. Org. Chem.*, **12**, 792 (1947).
[320] Soule, *J. Am. Chem. Soc.*, **47**, 981 (1925).
[321] Feigl, Miranda and Spinelli, *Ministerio agr., Dept. nacl. producao mineral, Lab. producao mineral Brazil, Chem. Investigations, Bol*, **11**, 79 (1943); *C. A.*, **40**, 3427 (1946).
[322] Feigl and Feigl, *Anal. Chim. Acta*, **3**, 300 (1949); *C. A.*, **43**, 8956 (1949).
[323] Duval and Duval, *Anal. Chim. Acta*, **5**, 71 (1951); *C. A.*, **45**, 3757 (1951).
[324] Griffing and Mellon, *Anal. Chem.*, **19**, 1017 (1947).
[325] Schlenk and Thal, *Ber.*, **46**, 2840 (1913).
[326] Mironescu and Ioanid, *Bul. soc. chim. Romania*, **15**, 49 (1933); *C. A.*, **28**, 146 (1934).
[327] Japp and Hooker, *J. Chem. Soc.*, **45**, 672 (1884).

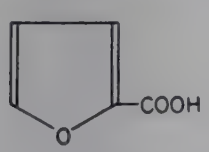
produces furoin.[300] When heated for 7–8 hours with a primary aromatic amine and its hydrochloride, furil undergoes resinification. Under somewhat milder conditions, it is reported that one of the furan rings is cleaved, and subsequent cyclization occurs with the formation of 1-aryl-2-furoyl-3-hydroxypyridinium chlorides.[42]

Benzfuril: (furylphenylglyoxal); $C_4H_3O—CO—CO—C_6H_5$; m.p. 41°. By oxidation of furobenzoin using copper sulfate in aqueous alcohol.[287] In aqueous alkali it is readily converted to benzfurilic acid.[287, 309] With cold bromine it forms a **tetrabromide,** m.p. 127–128°.[287] Treatment with nitromethane and sodium ethoxide cleaves benzfuril and produces ethyl furoate, ethyl benzoate, 2-(2-nitrovinyl)furan and ω-nitrostyrene.[316]

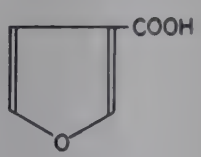
Chapter 12

FURANCARBOXYLIC ACIDS

In the carboxylic acids of the furan series one may consider the carboxyl as being linked directly to the nucleus (the furancarboxylic acids) or to a substituent group such as methyl (the furylalkanoic acids), vinyl (the furylalkenoic acids), etc.



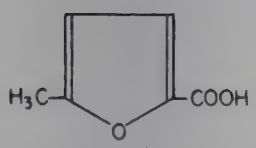
2-furoic acid



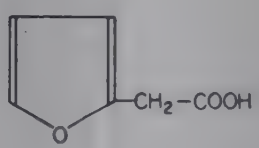
3-furoic acid



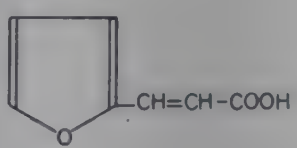
2,5-furandicarboxylic acid



5-methyl-2-furoic acid



2-furylacetic acid



3-(2-furyl)acrylic acid

All of the first class and their derivatives, with the exception of the nuclear nitro and halo-substituted compounds, are discussed in this chapter. The others form the subject matter of Chapter 13.

2-Furoic Acid

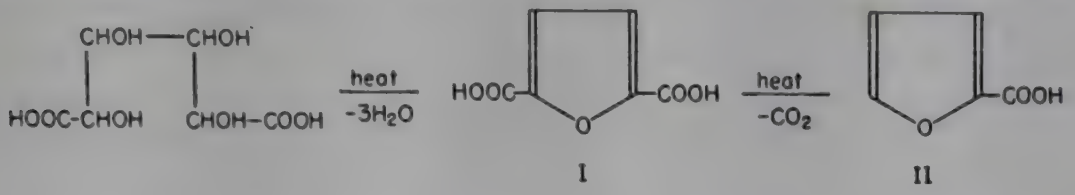
Preparation

2-Furoic acid bears the distinction of being the earliest isolated compound of the furan series. Its former designation as pyromucic acid was a natural consequence of its original derivation from mucic acid by the action of heat.[1] Since Scheele's discovery of the product, other workers have prepared it by similar procedures from mucic acid[2,3,4,5,6,7,8] and from other car-

[1] Scheele, "Sämtliche Physische und Chemische Werke", Vol. II, p. 265, Berlin, compiled by Hermbstädt, 1793.
[2] Houtou-Labillardière, *Ann. chim. phys.* (*2*), **9**, 365 (1818).
[3] Limpricht, *Ann.*, **165**, 253 (1873).
[4] Klinkhardt, *J. prakt. Chem.*, **25**, 41 (1882).
[5] Schmitt and Cobenzl, *Ber.*, **17**, 599 (1884).
[6] Kent and Tollens, *Ann.*, **227**, 221 (1885).
[7] Zenoni, *Gazz. chim. ital.*, **20**, 517 (1890).
[8] Chavanne, *Bull. soc. chim.* (*3*), **29**, 337 (1903).

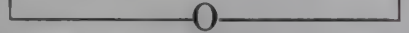
bohydrate materials such as saccharic acid,[9] iso-saccharic acid,[10, 11] chondrosic acid,[12] and arabic acid[13, 14]

From mucic and saccharic acids, the reaction proceeds by way of the intermediate formation of 2,5-furandicarboxylic acid ("dehydromucic acid"), I, which undergoes thermal decomposition with loss of carbon dioxide to give 2-furoic acid, II.[15, 16, 17, 18, 11, 9, 19] The yield of furoic acid is poor, and



I II

among the by-products of the reaction, is an isomeric compound first isolated by Limpricht,[3] and named "isopyromucic acid." This was assigned the lactone structure, CH=CH—CH_2—CO—CO (see also [9, 8]), but Zenoni[7]



failed to isolate this product from the reaction mixture.

Alkaline potassium ferricyanide has been suggested for the oxidation of furan methyl groups to carboxyl.[20] In this way 2-methyl- and 2,5-dimethylfuran were converted to the corresponding carboxy- and dicarboxyfurans, albeit in very poor yields. The difficulty in such reactions is to find a reagent vigorous enough to accomplish the desired oxidation of the side chain, yet mild enough to leave the nucleus intact. Such reagents as chromic and nitric acids, which are applicable in the benzene series, are too harsh when applied to the simple homologs of furan. By use of potassium ferricyanide, 2-furoic acid was also obtained from 2-vinylfuran, furfuryl alcohol, 2-furyl methyl ketone and furil.[20]

The most convenient, and best starting material for the preparation of 2-furoic acid is, of course, the readily available furfural. Disproportionation of the latter to the acid and furfuryl alcohol by the Cannizzaro reaction is discussed elsewhere (p. 379). However, certain disadvantages of this method of preparation should be mentioned. In the first place, two moles of furfural are required for each mole of furoic acid produced. Even more serious, how-

[9] Sohst and Tollens, *Ann.*, **245**, 1 (1888).
[10] Tiemann, *Ber.*, **17**, 241 (1884).
[11] Tiemann and Haarmann, *Ber.*, **19**, 1257 (1886).
[12] Levene and LaForge, *J. Biol. Chem.*, **20**, 433 (1915).
[13] Fischer and Piloty, *Ber.*, **24**, 4214 (1891).
[14] Chavanne, *Ann. chim. phys.* (*8*), **3**, 507 (1904).
[15] Malaguti, *Ann. chim. phys.* (*2*), **63**, 86 (1836).
[16] Fittig and Heinzelmann, *Ber.*, **9**, 1198 (1876).
[17] Heinzelmann, *Ann.*, **193**, 184 (1878).
[18] Seelig, *Ber.*, **12**, 1081 (1879).
[19] Hill, *Am. Chem. J.*, **25**, 439 (1901).
[20] Brown, *Iowa State Coll. J. Sci.*, **11**, 227 (1937).

ever, is the problem of separating the acid from the furfuryl alcohol which is formed simultaneously. Due to the ready resinification of the alcohol, isolation of the acid in a pure state generally entails a considerable sacrifice in yield, although it is reported that if furoic acid is used to neutralize the excess alkali this difficulty is minimized.[21]

Several of the common oxidizing agents have been used for oxidizing furfural to the acid. Chromic acid was employed by Hurd *et al.*,[21] but the reported yield could not be duplicated in later work.[22] It is preferable to employ a neutral or alkaline medium in order to minimize nuclear oxidation. Yields in the neighborhood of 80 per cent have been obtained using alkaline potassium permanganate under mild temperature conditions.[23, 24, 25] With sodium peroxide suspended in carbon tetrachloride, a 90 per cent yield has been reported.[26] Schwanert[27, 28] and others[3, 29, 30] oxidized furfural with the stoichiometric amount of silver oxide, but later, Dinelli[31] showed that the quantity of costly silver oxide could be decreased to catalytic amounts when employed in conjunction with cupric oxide. In this procedure, furfural is added to a boiling suspension of cupric oxide and a small amount of silver oxide in dilute, aqueous, sodium hydroxide. The cupric oxide is reduced to the cuprous form, two moles of the former being required per mole of furfural to be oxidized. Furoic acid may be isolated in approximately 90 per cent yield. Dinelli[31] applied the same method on oxidizing β-2-furylacrolein to the corresponding acid.

$$C_4H_3O\text{—}CHO + 2\ CuO \xrightarrow[[OH^-]]{[Ag_2O]} C_4H_3O\text{—}COOH + Cu_2O$$

Since the cuprous oxide can be reoxidized to the cupric state by contact with air or oxygen, the development of a completely catalytic process for large scale production of furoic acid from furfural was possible.[32] By the continuous passage of oxygen through the mixture, the oxides function as a true catalyst and not merely as a reactant. It was also found that several other base metal oxides (those of Ti, Ce, Th, Fe, Co, Ni, Bi and Sb) could be substituted for cupric oxide. Similarly, the oxides of gold, platinum or

[21] Hurd, Garrett and Osborne, *J. Am. Chem. Soc.*, **55**, 1082 (1933).
[22] Hurd and Li, private communication.
[23] Volhard, *Ann.*, **261**, 379 (1891).
[24] Freundler, *Bull. soc. chim.* (*3*), **17**, 609 (1897).
[25] Frankland and Aston, *J. Chem. Soc.*, **79**, 511 (1901).
[26] Schneider, Dissertation, University of Zurich, 1931.
[27] Schwanert, *Ann.*, **114**, 63 (1860).
[28] Schwanert, *Ann.*, **116**, 257 (1860).
[29] Hill and Jennings, *Am. Chem. J.*, **15**, 158 (1893).
[30] Delepine and Bonnet, *Bull. soc. chim.* (*4*), **5**, 879 (1909).
[31] Dinelli, *Ann. chim. applicata*, **19**, 448 (1939); *C. A.*, **34**, 1903 (1940).
[32] Dunlop, (to The Quaker Oats Co.), U. S. Pat. 2,407,066 (1942); *C. A.*, **41**, 780 (1947).

palladium can assume the function of silver oxide, without which the base metal oxides are completely inactive. On the other hand, when used in sufficient quantity, the noble metal oxides may be employed alone[33] (see also [33a]), although this is less preferable economically than the mixed oxide catalyst. In either case, the oxidation is carried out in aqueous, alkaline medium, and complications due to the Cannizzaro reaction are minimized by incremental addition of the furfural, and by vigorous agitation to insure, at all times, intimate contact of furfural, catalyst and oxygen.

General Properties

2-Furoic acid is a white, crystalline solid which melts at 133°. It is very stable under normal storage conditions, and is not prone to discoloration on standing as are many other furan compounds. As a consequence of this stability, the ease of purification of the acid, and its low hygroscopicity, furoic acid is suitable for use as an acidimetric standard.[34] It is sparingly soluble in cold water, but the solubility increases rapidly with temperature as shown in Table 1. Other solvents include alcohol, ether, benzene and chlorinated hydrocarbons. The partition coefficient of furoic acid between water and ether, C_w/C_e, is approximately 0.25 at 25° although it varies to a certain extent depending upon the concentration of acid.[35, 36]

Kaufmann[43, 44] (see also [45]) reports furoic acid (0.5 per cent) to be germicidal for *E. coli* in five minutes; and for *S. aureus* at yet higher concentrations. Several alkylfuroic acids have also been shown to be germicidal[46, 47] (see also [48]). The bacteriostatic activity of furan types including furoic acid and its derivatives was investigated by Dodd *et al.*[49]; for trypanocidal

[33] Isenhour, (to The Quaker Oats Co.), U. S. Pat. 2,041,184 (1936); *C. A.*, **30**, 4515 (1936).
[33a] Andrisano, *Boll. sci. facoltà chim. ind. Bologna*, **7**, 66 (1949); *C. A.*, **44**, 9404 (1950).
[34] Kellog and Kellog, *Ind. Eng. Chem., Anal. Ed.*, **6**, 251 (1934).
[35] Dermer, Markham and Trimble, *J. Am. Chem. Soc.*, **63**, 3524 (1941).
[36] Dermer and Dermer, *J. Am. Chem. Soc.*, **65**, 1653 (1943).
[37] Berthelot and Rivals, *Ann. chim. phys.* (7), **7**, 29 (1896).
[38] André, *Compt. rend.*, **128**, 1035 (1899).
[39] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).
[40] Parks, Mosley and Peterson, *J. Chem. Phys.*, **18**, 152 (1950).
[41] The Quaker Oats Co., unpublished work.
[42] Gilman, Janney and Bradley, *Iowa State Coll. J. Sci.*, **7**, 429 (1933).
[43] Kaufmann, *Ber.*, **55**, 289 (1922).
[44] Kaufmann, *Ber. pharm. Ges.*, **33**, 132 (1923).
[45] Miner, (to The Quaker Oats Co.), U. S. Patent 1,554,642 (1925).
[46] Phatak and Laake, *J. Pharmacol. Exptl. Therap.*, **58**, 155 (1936).
[47] Calloway, Gilman and Werkman, *Proc. Iowa Acad. Sci.*, **40**, 81 (1933); *C. A.*, **29**, 2661 (1935).
[48] Feasley, Gwynn, Degering and Tetrault, *J. Am. Pharm. Assoc.*, **30**, 41 (1941).
[49] Dodd, Cramer and Ward, *J. Am. Pharm. Assoc.*, **39**, 313 (1950).

TABLE 1. PROPERTIES OF 2-FUROIC ACID

		Ref.
Thermochemical data in kg.-cal. per mole:		
Heat of formation:		
from elements	115.7, 121.4, 119.14	37, 38, 39, 40
from furfural	66.0	37
Heat of combustion:		
at constant volume	494.4, 488.4, 487.75	37, 39, 40
at constant pressure	493.4, 488.1	37, 39
Heat of sublimation	19.1	41
Vapor pressure data:		41

Temp. (°C.)	P (mm. Hg)
96	1.8
99	2.1
105	3.1
110	4.4
118	7.1
121	8.4
127	12.5
129	14.3
133 (melting point)	17.8
139	26.0

Decarboxylation temperature, 158°	42
Solubility in water:	41

Temp. (°C.)	Solubility (g./100 g. H_2O)
20	3.6
30	5.8
40	12.4
50	27
60	60
70	133
80	335

action, see Ziering and Buck.[50] The physiological effects of sodium furoate on various animals was studied by Fujii[51]; of furamide, by Lott and Christianson,[52] and by Gibbs and Reichert.[53] Furoic acid derivatives have been tested as insecticides,[54, 55] and for their fungicidal and fungistatic activity.[56]

[50] Ziering and Buck, *Jubilee Vol. Emil Barell*, **1946**, 378; *C. A.*, **42**, 3533 (1948).

[51] Fujii, *Folia japon. pharmacol.*, **1**, 15 (1925); *Ber ges. Physiol. exptl. Pharmacol* **37**, 904 (1926); *Chem. Centr.*, **1927, I**, 2097.

The furan nucleus exerts a stronger polarizing influence than that of benzene as indicated by comparison of the dissociation constants of 2-furoic and benzoic acids ($K_i = 7 \times 10^{-4}$ and 6×10^{-5}, respectively). In Table 2 are listed the dissociation constants of a number of furan acids as calculated from pH measurements. As expected, negative substituents increase the degree of ionization.

Furoic acid sublimes readily, the vapor being very irritating to the nose and throat, producing sneezing and coughing. Vapor pressure measurements, by a static method, gave the results listed in Table 1. From these data the following equation was derived, relating vapor pressure to absolute temperature.

$$\log P_{(mm)} = -\frac{4183}{T^\circ} + 11.563$$

Differentiation of the above equation with respect to T, and substitution of the dP/dT value in the Clausius-Clapeyron equation shows the heat of sublimation of 2-furoic acid to be in the neighborhood of 19.1 kg.-cal./mole.

Salts: Schmelz and Beilstein[60] prepared a number of metal 2-furoates and noted that the sodium, potassium, calcium and copper salts were water-soluble. The lead salt was found to be difficultly soluble in cold water; soluble in hot water. Manganous 2-furoate is very soluble in cold water, forming a trihydrate; insoluble in absolute alcohol and in acetone.[21] For iron salts, see Weinland and Paschen.[61]

The rare earth metal salts, yttrium, lanthanum and terbium 2-furoates, were prepared by Grant and James.[62] The europium salt is described by James and Robinson.[63]

Vanadyl 2-furoate.[64]

Uranyl 2-furoate, lemon-yellow leaflets, easily soluble in water; insoluble in alcohol and ether.[65]

Triethyllead 2-furoate, m.p. 153–154°, was obtained by Gilman and Robinson[66] who also prepared the corresponding salt of 3-(2-furyl)acrylic acid. See Gilman and Gruhzit[67] for toxicity measurements and effect of this salt on the nervous system.

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[52] Lott and Christiansen, *J. Am. Pharm. Assoc.*, **23**, 788 (1934).
[53] Gibbs and Reichert, *Am. Chem. J.*, **13**, 289 (1891).
[54] O'Kane, private communication to Crop Protection Institute, 1932.
[55] Yeager, Wooley and Brown, *Proc. Soc. Exptl. Biol. Med.*, **30**, 19 (1932).
[56] Borzini and Marini-Bettolo, *Ricerca sci.*, **10**, 878 (1939); *C. A.*, **34**, 4853 (1940); *Bol. staz. patol. vegetale*, **18**, 347 (1940); *C. A.*, **35**, 564 (1941); Borzini and Ciferri, *Ist. botan. univ. lab. crittogam. Pavia Atti (5)*, **3**, 243 (1947); *C. A.*, **43**, 8595 (1949).
[57] Catlin, *Iowa State Coll. J. Sci.*, **10**, 65 (1935).
[58] German, Jeffery and Vogel, *J. Chem. Soc.*, **1937**, 1604.
[59] Ostwald, *Z. phys. Chem.*, **3**, 369 (1889).
[60] Schmelz and Beilstein, *Ann. suppl.*, **3**, 275 (1864).
[61] Weinland and Paschen, *Z. anorg. Chem.*, **92**, 81 (1915).
[62] Grant and James, *J. Am. Chem. Soc.*, **37**, 2652 (1915).
[63] James and Robinson, *J. Am. Chem. Soc.*, **35**, 754 (1913).
[64] Prebluda, U. S. Patent 2,135,111 (1939); *C. A.*, **33**, 1104 (1939).
[65] Müller, *Z. anorg. Chem.*, **109**, 235 (1920); *Chem. Centr.*, **1920**, III, 414.
[66] Gilman and Robinson, *Rec. trav. chim.*, **49**, 766 (1930).
[67] Gilman and Gruhzit, *J. Pharmacol. Exptl. Therap.*, **41**, 1 (1931).

Phenylmercuric 2-furoate, m.p. 115°.[68] Highly potent germicide, suggested for use in soaps and ointments.
Dodecylammonium 2-furoate, m.p. 72.5–73°.[69] Octadecylammonium 2-furoate, m.p. 91–92°.[69] N,N′-diphenylformamidine 2-furoate, m.p. 144°.[70] S-1-naphthylmethylthiouronium 2-furoate, m.p. 220°.[71] Piperazinium 2-furoate, m.p. 234–236° (dec.).[71a]

The heterocyclic oxygen atom exerts a loosening effect on carboxyl groups attached to the furan ring. Thus, carboxyfurans in general may be decar

Table 2. Dissociation Constants of Furan Acids*

Acid	$K_i \times 10$
2-Furoic	75.2†
3-Chloro-2-furoic	204.1
5-Chloro-2-furoic	147.4
3,4-Dichloro-2-furoic	400.3
3,5-Dichloro-2-furoic	377.4
4,5-Dichloro-2-furoic	248.6
5-Bromo-2-furoic	144.3
3,5-Dibromo-2-furoic	326.8
5-Iodo-2-furoic	116.0
5-Nitro-2-furoic	870
5-Methyl-2-furoic	38.1
3-Furoic	11.3
2-Methyl-3-furoic	2.9
2,4-Dimethyl-3-furoic	2.8
2,5-Dimethyl-3-furoic	2.3
3-(2-Furyl)acrylic	3.8

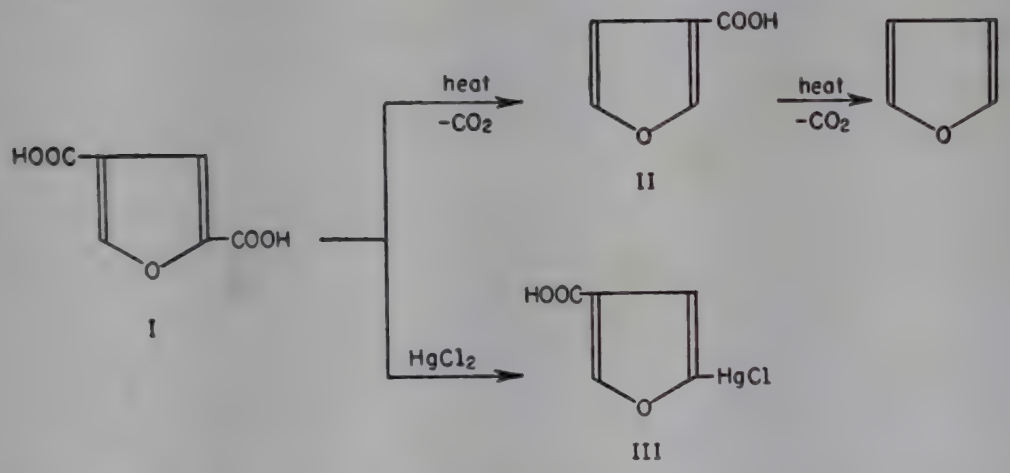
* Taken from Catlin.[57]
† Values of 67.7 and 69.9 $\times 10^{-5}$ are reported by German *et al.*[58] (see also [59]).

boxylated comparatively easily, a property which has been useful for t synthesis of many furans. As a matter of fact, the decarboxylation of furoic acid constitutes the best available method for the laboratory prepa tion of furan. This was earlier accomplished by the dry distillation of me

[68] Andersen, (to Lever Brothers Co.), U. S. Patent 2,022,997 (1936); *C. A.*, **30**, (1936).
[69] Hunter, *Iowa State Coll. J. Sci.*, **15**, 223 (1941).
[70] Knott, *J. Chem. Soc.*, **1945**, 686.
[71] Bonner, *J. Am. Chem. Soc.*, **70**, 3508 (1948).
[71a] Prigot and Pollard, *J. Am. Chem. Soc.*, **70**, 2758 (1948).

furoates,[a, 73, 3, 74, 24, 75] or by simply heating the free acid in a sealed tube,[74, 24, 76] but more convenient modifications are now available.[77, 78] A study of the decarboxylation of several furancarboxylic acids in hydrochloric acid is reported by Machida.[79]

The greater lability of alpha as compared to beta carboxyl groups is indicated by the preferential thermal decarboxylation of 2,4-furandicarboxylic acid, I, over copper-bronze to give 3-furoic acid, II, in 75–80 per cent yield[80] (see also [81]). Subjection of furantetracarboxylic acid to partial decarboxylation shows stepwise removal of —COOH in the order α, α', β with formation of the corresponding tri-, di- and monocarboxylic acids.[82] Another illustration of the comparative stability of the bonds connecting alpha and beta carboxyls to the nucleus is the preferential rupture of the former by the action of mercuric chloride. With this reagent, the disodium salt of 2,4-furandicarboxylic acid gives rise to 4-carboxy-2-furylmercuric chloride, III.[80] The latter reaction appears to be applicable with all α-furan-



carboxylic acids, but not for the replacement of β-carboxyl groups. By employing the free acid instead of the sodium salt, the reaction becomes

[a] In the gases evolved during the dry distillation of sodium, calcium, and barium 2-furoates with or without soda-lime, Hurd and Pilgrim[72] found a small amount of methylacetylene and an insignificant quantity of cyclopropene (see also [24]).

[72] Hurd and Pilgrim, *J. Am. Chem. Soc.*, **55**, 1195 (1933).

[73] Limpricht, *Ber.*, **3**, 90 (1870).

[74] Freundler, *Compt. rend.*, **124**, 1157 (1897).

[75] Hartley and Dobbie, *J. Chem. Soc.*, **73**, 598 (1898).

[76] Bourgignon, *Bull. soc. chim. Belg.*, **22**, 87 (1908); *Chem. Centr.*, **1908, I**, 1630.

[77] Gilman and Lousinian, *Rec. trav. chim.*, **52**, 156 (1933).

[78] Gilman and Blatt, "Organic Syntheses," Collective Vol. I, 2nd Ed., p. 274, New York, John Wiley and Sons, 1941.

[79] Machida, *J. Chem. Soc. Japan*, **64**, 1311 (1943); *C. A.*, **41**, 4482 (1947).

[80] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

[81] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 268 (1932).

[82] Reichstein, Grüssner, Schindler and Hardmeier, *Helv. Chim. Acta*, **16**, 276 (1933).

one of simple α-decarboxylation, and the intermediate mercurial is not isolated.[83, 84]

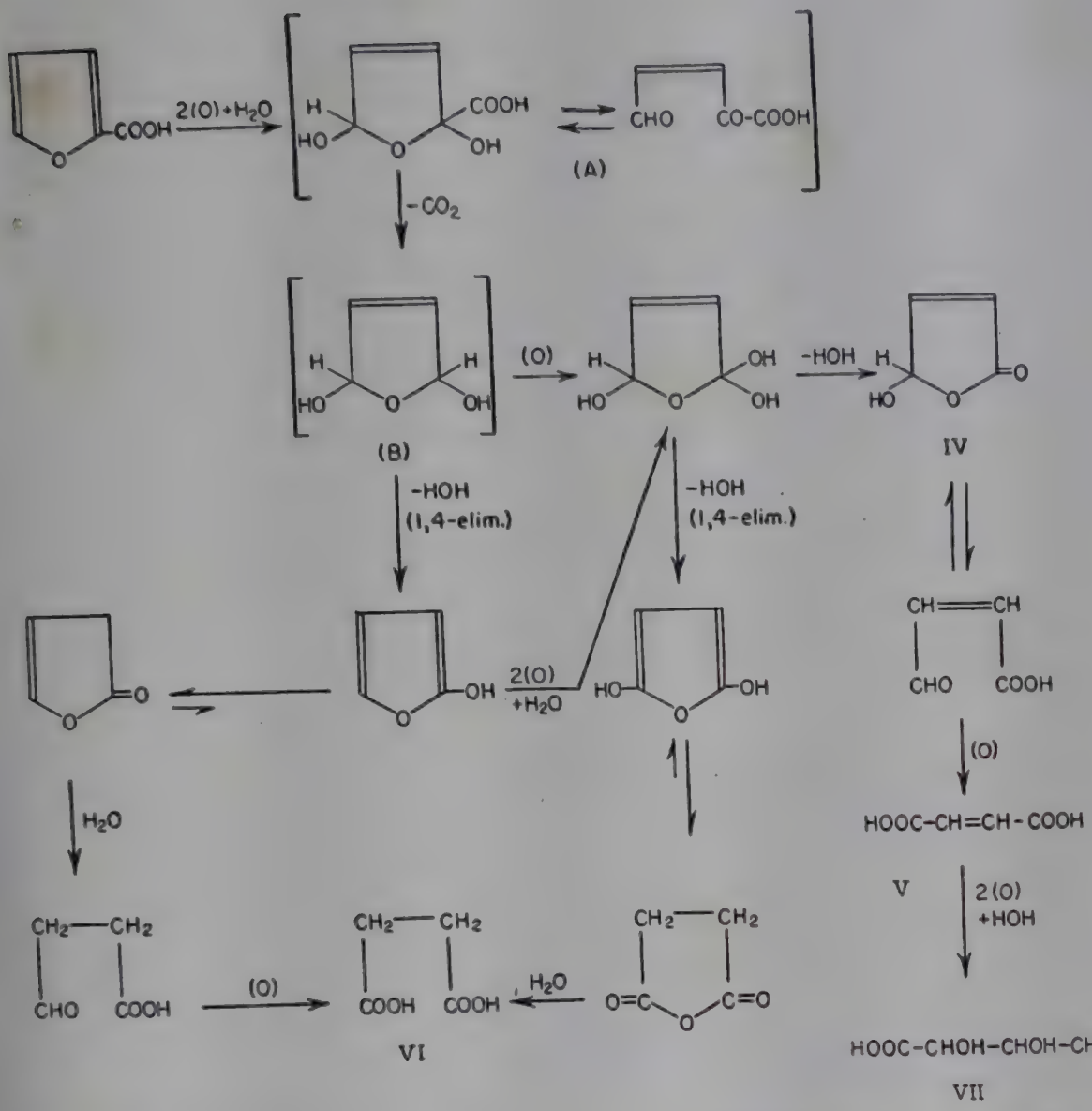
Gilman and his students[42] determined the decarboxylation temperatures of a number of furan acids using the Norris graphical method. Unfortunately, secondary decomposition reactions interfered in many instances, thereby complicating the measurements and, to a large extent, nullifying attempts to correlate the results with structure, nature of substituent groups, and the like.

The stability of the furan ring toward acidic reagents is greatly increased by the presence of nuclear carboxyl groups. Unlike furan compounds with less negative substituents, the furancarboxylic acids may be nitrated and sulfonated directly. The usual catalysts may be employed in esterification reactions with no special precautions. Exposure to the condensing agents commonly used in the Friedel-Crafts reaction fails to produce the deep-seated decomposition observed with furan and its homologs, so that 2-furoic esters, for example, can be alkylated smoothly by this procedure. Of course, sufficiently harsh acidic conditions, notably where the halogen acids are involved, may bring about complete destruction. Thus, 2-furoic acid is transformed into a resinous mass when heated with hydriodic acid at 140°.[85, 3]

Furoic acid gives iodine and thiocyanogen numbers which are only a small fraction of the calculated values.[86]

Oxidation of furoic acid generally results in loss of the carboxyl group and opening of the furan nucleus. Limpricht[3] reported β-formylacrylic acid (malealdehydic acid), IV, as the product formed with chromic acid or with lead dioxide in dilute sulfuric acid. IV was also detected (as the phenylhydrazone) in the solution resulting from exposure (several months) of aqueous furoic acid to oxygen in the sunlight,[87] and has been shown to be an intermediate product when furoic acid is oxidized electrolytically in dilute sulfuric acid.[88] On warming furoic acid with Caro's acid, Asahina[89] obtained a mixture of maleic and fumaric acids, V, together with some succinic acid, VI. Obata[90] likewise derived maleic acid from furoic acid by the action of alkaline permanganate, and Milas[91] reports fumaric acid as

[83] Gilman and Wright, *J Am. Chem. Soc.*, **55**, 3302 (1933).
[84] Gilman and Vander Wal, *Rec. trav. chim.*, **52**, 267 (1933).
[85] Wichelhaus, *Ann.*, **152**, 257 (1869).
[86] Caldwell and Piontkowski, *J Am. Chem. Soc.*, **56**, 2086 (1934).
[87] Ciamician and Silber, *Ber.*, **46**, 1558 (1913).
[88] Hellström, *Svensk Kem. Tid.*, **60**, 214 (1948); *C. A.*, **43**, 1271 (1949).
[89] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta. Phytochim.*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).
[90] Obata, *J. Agr. Chem. Soc. Japan*, **16**, 187 (1940); *C. A.*, **34**, 5840 (1940).
[91] Milas, *J. Am. Chem. Soc.*, **49**, 2005 (1927).



the major product when the oxidation is carried out with aqueous chlorate ion in the presence of vanadium pentoxide. In another experiment with chlorate ion, using osmium tetroxide as the catalyst, oxidation proceeded yet further to give *meso*-tartaric acid, VII, together with some oxalic acid.[91] The formation of these products can be explained by postulating the initial step of reaction as a 1,4-type hydroxylation of the furan nucleus to form the intermediate (A). As a vinylog of a β-carbonyl carboxylic acid, (A)

[92] Jones and Imperial Chemical Industries Ltd., British Patent 595,041 (1947); *C. A.*, **42**, 2992 (1948).

[93] Jones (to Imperial Chemical Industries Ltd.), U. S. Patent 2,475,097 (1949); *C. A.*, **43**, 7970 (1949).

[94] Baeyer, *Ber.*, **10**, 1358 (1877).

[95] Fecht, *Ber.*, **38**, 1272 (1905).

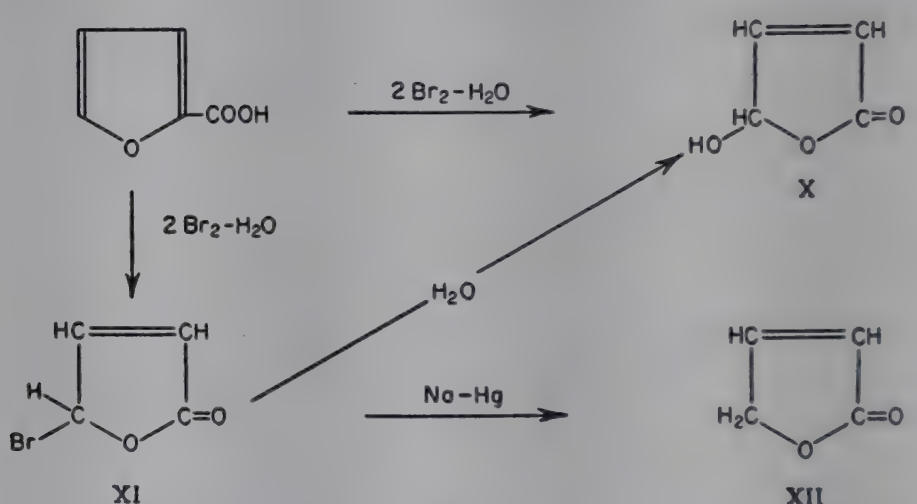
[96] Hill and Hendrickson, *Ber.*, **23**, 452 (1890).

[97] Hill and Cornelison, *Am. Chem. J.*, **16**, 188 (1894).

[98] Tonnies, *Ber.*, **12**, 1202 (1879).

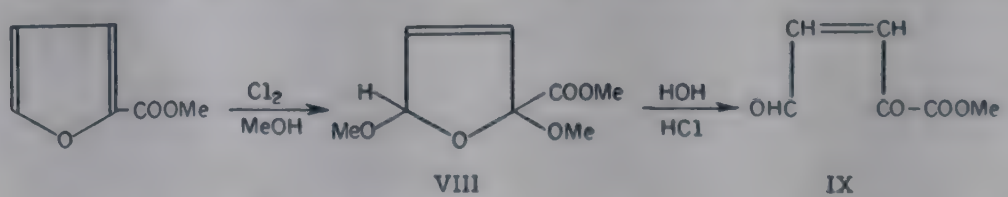
would be expected to lose carbon dioxide[b] with great ease to give rise to 2,5-dihydroxy-2,5-dihydrofuran (B), a cyclic, hydrated form of malealdehyde (compare oxidation of furfural, Chapter 9).

With aqueous chlorine or bromine, oxidation proceeds similarly, although the nature of the final products is dependent upon the experimental conditions. It was demonstrated by Limpricht[3] (see also [94, 95, 87]) that if only two moles of bromine are employed per mole of aqueous furoic acid, β-formylacrylic acid (shown in the hemiacylal form, X) is obtained. The homologous 5-methyl-2-furoic acid is attacked similarly with formation of β-acetylacrylic acid.[96, 29] In another experiment with furoic acid, Limpricht[3] isolated a compound $C_4H_3BrO_2$, m.p. 84°, which was reduced with sodium amalgam to $C_4H_4O_2$. He did not identify either of the products, but in view of the work of Hill and Cornelison[97] (see also p. 118), it is reasonable to suppose that the first is γ-bromo-γ-crotonolactone, XI, which on reduction would give γ-crotonolactone, XII, $C_4H_3O_2$. The reactions involved are indicated below.



The early work of Schmelz and Beilstein[60] (see also [98]) showed that the vigorous action of greater proportions of bromine resulted in the formation

[b] Consistent with this viewpoint is the fact that no C_5 compounds have ever been reported among the products of oxidation of furoic acid. By contrast, several C_6 compounds have been isolated, generally in the form of derivatives, as intermediate products of the oxidation of furfural (Chapter 9). On the other hand, furoic ester is oxidizable to a C_5 compound by the action of alcoholic halogen. Thus, Jones[92, 93] reports the formation of methyl 2,5-dimethoxy-2,5-dihydrofuroate, VIII, from methyl furoate and chlorine in methanol in the presence of sodium carbonate. Hydrolysis of VIII gives rise to 2,5-dioxo-3-pentenoic ester (ketoglutaconaldehydic ester), IX.



VIII IX

of α,β-dibromo-β-formylacrylic acid (dibromomalealdehydic acid), XIII. This product and its chlorine analog, the so-called mucobromic and mucochloric acids, were later prepared by Hill and his students[99, 100, 101, 102, 103] who demonstrated that the yield is influenced by the amount of water present, and to a greater extent by the rate of addition of the halogen (bromine or chlorine). Thus, slow addition of bromine[60, 3] gave only a 25 per cent yield of XIII, whereas rapid addition to aqueous furoic acid, followed by a short heating period gave the desired product in 70 per cent yield. By employing a somewhat lower proportion of water, Johnson[104] was able to increase this yield to 75–80 per cent of the theoretical. It is of interest to observe that, during the recent war, attention was given to the

$$C_4H_3O\text{—}COOH \xrightarrow[HOH]{> 4\ Br_2} OHC\text{—}CBr{=}CBr\text{—}COOH \xrightarrow{NaNO_2}$$

XIII

$$HOOC\text{—}C(CHO){=}NO_2Na \xrightarrow{HCl} 1,3,5\text{-}C_6H_3(NO_2)_3$$

XIV

synthesis of trinitrobenzene from furoic acid.[104] This had been accomplished earlier by Hill and Torrey[105] who converted XIII to sodium *aci*-nitromalonaldehyde, XIV, in 25 per cent yield by treatment with aqueous sodium nitrite. On acidification with hydrochloric acid, the free nitromalonaldehyde which is formed undergoes cyclization with loss of carbon dioxide to give 1,3,5-trinitrobenzene in 20–25 per cent yield. The low, over-all yield from 2-furoic acid renders the method impractical. Alkaline fission of α,β-dichloro-β-formylacrylic acid to obtain dichloroacrylic acid is discussed by Hill.[100, 102]

Stalmann and Kolbe[106] reported the reduction of 2-furoic acid to furfuryl alcohol by the action of sodium amalgam, but no details are given, other than the observation that the alcohol obtained was insoluble in water. On the other hand, Schmelz and Beilstein[60] and Yoder and Tollens[107] state that sodium amalgam fails to effect reduction of the acid or its esters. Additional attempts by the latter investigators, using aluminum, zinc and tin in either acidic or alkaline medium, yielded only resins and unchanged furoic acid.

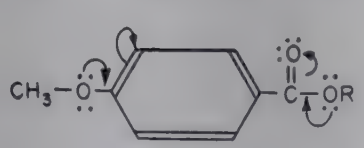
[99] Jackson and Hill, *Ber.*, **11**, 1671 (1878).
[100] Hill and Bennett, *Ber.*, **12**, 655 (1879).
[101] Hill, *Am. Chem. J.*, **3**, 33 (1881).
[102] Hill, *Am. Chem. J.*, **3**, 165 (1881).
[103] Hill and Allen, *Am. Chem. J.*, **19**, 650 (1897).
[104] Johnson, "Preparation of Nitro Compounds," PB No. **31092**, U. S. Dept. Commerce, 1941.
[105] Hill and Torrey, *Am. Chem. J.*, **22**, 89 (1899); *Ber.*, **28**, 2597 (1895).
[106] Stalmann and Kolbe, *Zeitschrifte für Chemie* (*3*), **10**, 47 (1867).
[107] Yoder and Tollens, *Ber.*, **34**, 3447 (1901).

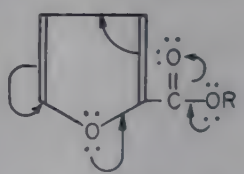
More recently, however, Nystrom and Brown[108] have reported the isolation of furfuryl alcohol in 85 per cent yield by reduction of the acid with lithium aluminum hydride. Catalytic hydrogenation is discussed elsewhere (Chapter 15).

Nuclear Syntheses

By the action of dry bromine or chlorine, 2-furoic acid forms addition products and halogen substituted acids as discussed in Chapter 3. The preparation of the nitrofuroic acids is dealt with in Chapter 4. Sulfonation of furancarboxylic acids is taken up later in this chapter (p. 509). With the exception of metallation, the remaining nuclear substitution reactions are considered here.

The Friedel-Crafts and Related Reactions with Furancarboxylic Acids and Esters.[c] *Alkylation and Acylation.* In general, benzene derivatives possessing meta-directing substituents either react sluggishly or fail to participate in the Friedel-Crafts reaction as witnessed by the deactivating effect of the carbomethoxy group in hindering alkylation or acylation of methyl benzoate under the usual conditions. On the other hand, this effect is counteracted by certain other substituents, for example, a methoxy group in the *p*-position. Accordingly, methyl anisate alkylates readily with *i*-propyl chloride in the presence of aluminum chloride.[109] In view of this, it is not surprising to find that 2-furoic esters (and certain other furans possessing negative substituents) alkylate and acylate relatively easily, the internal etheric function in the nucleus neutralizing the influence of the carbalkoxy group. The analogy is evident from consideration of the resonance modifications, shown below, which depict the availability of electrons





at the position of substitution. When both α-positions of the furan ring are occupied by such groups, no reaction takes place. Thus, diethyl 2,5-furandicarboxylate was recovered unchanged following an attempt to alkylate with butyl chloride and aluminum chloride.[109]

Methyl and ethyl halides fail to alkylate methyl 2-furoate, but the higher alkyl halides react smoothly in most cases, the entering substituent going to the 5-position. The experimental conditions employed by Gilman and

$$C_4H_3O{-}COOCH_3 + (CH_3)_2CHCl \xrightarrow{AlCl_3} 2,5\text{-}C_4H_2O{-}[CH(CH_3)_2][COOCH_3]$$

[c] See Chapter 3 for application to halogen substituted furoic acids.

[108] Nystrom and Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

[109] Gilman and Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933).

Calloway[109] involve incremental addition of furoic ester and the alkyl halide to aluminum chloride (between one and two moles per mole of the reactants) in carbon disulfide at 0°. Ferric chloride[109] and hydrogen fluoride[110] have also been used successfully as condensing agents, and furoic acid may be substituted for the ester although the latter is preferred because of the greater ease of handling the reaction mixture.[109]

The reported data indicate that irrespective of the form of the alkyl halide employed, the alkyl group introduced into the nucleus possesses the most highly branched configuration (see also p. 122). Thus, each of the four isomeric butyl halides yielded some of the same product, methyl 5-*t*-butyl-2-furoate, when condensed with 2-furoic ester. As a matter of fact, this was the sole product isolated in each instance, even though the yield from *sec*-butyl bromide was less than two per cent.[109] However, the reaction mixtures presented some difficulty in fractionation, and the possibility may not be excluded that a mixture of isomeric butylfuroic esters was formed, particularly with *n*- or *sec*-butyl halides as the alkylating agents.

The configuration of the butyl substituent was established indirectly in the following manner.[109, 111] The methyl 5-butyl-2-furoate derived from *n*-butyl chloride and methyl 2-furoate was saponified to the free acid, melting at 104–105°. Decarboxylation gave 2-butylfuran which was mercurated to obtain 5-butyl-2-furylmercuric chloride. By comparison of melting points, the latter[d] was found to be unlike three other 5-butyl-2-furylmercuric chlorides (*n*-, *sec*- and *i*-butyl), each of which was synthesized by an unequivocal procedure. It follows that the ester obtained on alkylation with *n*-butyl chloride possesses a *t*-butyl substituent, and that the same ester results on alkylation with *sec*-, *i*- and *t*-butyl halides, since in each instance, hydrolysis gives the acid melting at 104–105°.

$$C_4H_3O\text{—}COOCH_3 \xrightarrow[(AlCl_3)]{\text{n-, i-, sec-, or } t\text{-}C_4H_9X} 2,5\text{-}C_4H_2O\text{—}(t\text{-}C_4H_9)(COOCH_3) \xrightarrow{HOH} \xrightarrow{-CO_2}$$

$$C_4H_3O\text{—}C_4H_9(t) \xrightarrow{HgCl_2} 2,5\text{-}C_4H_2O\text{—}(t\text{-}C_4H_9)(HgCl)$$

n-Pentyl chloride likewise undergoes extensive rearrangement when con-

[d] Gilman and Calloway[109] list 136–137° as the melting point of 5-*t*-butyl-2-furylmercuric chloride, whereas the m.p. 174–175° is given in a later article.[112] Further work with the compound has confirmed the latter value,[113] indicating that Gilman and Calloway were working with an impure product. However, since the other three butyl derivatives all melted below 100°, there is little doubt that the compound obtained by Gilman and Calloway was the *t*-butyl isomer.

[110] Simons, Archer and Passino, *J. Am. Chem. Soc.*, **60**, 2956 (1938).

[111] Gilman, Henry, private communication.

[112] Gilman and Burtner, *J. Am. Chem. Soc.*, **57**, 909 (1935).

[113] Burtner, R. R., private communication.

densed with 2-furoic ester. On the basis of their experience with the butyl halides, Gilman and Calloway[109] suggested that the ester so obtained was probably methyl 5-*t*-pentyl-2-furoate. The correctness of this postulate is attested by the later work of Reichstein and co-workers.[114] On alkylation of methyl 2-furoate with *t*-pentyl chloride, these investigators isolated an ester, and on hydrolysis an acid, the physical properties of which check closely with those reported by Gilman and Calloway for the corresponding products obtained using *n*-pentyl chloride. On oxidation of the free acid with alkaline permanganate, dimethylethylacetic acid was formed in 79 per cent yield, the identity of which was proven by independent synthesis as shown below.[114] Thus, there appears to be little question that the same product, 5-*t*-pentyl-2-furoic ester, is formed on alkylation with either *n*- or *t*-pentyl chloride.

$$C_4H_3O{-}COOCH_3 \xrightarrow[AlCl_3]{n\text{- or } t\text{-}C_5H_{11}Cl} 2,5\text{-}C_4H_2O{-}(C[C_2H_5][CH_3]_2)(COOCH_3)$$

$$\downarrow \text{HOH}$$

$$\downarrow (O)$$

$$t\text{-}C_5H_{11}Cl \xrightarrow{Mg} \xrightarrow{CO_2} (CH_3)_2(C_2H_5)C{-}COOH$$

By analogy, the 5-hexyl-2-furoic ester obtained by reaction of methyl 2-furoate with *n*-hexyl bromide[109] is probably also a branched chain type.

TABLE 3. ALKYLATION OF 2-FUROIC ESTERS

2-Furoic ester (0.1 mole)	Alkyl halide (0.1 mole)	Catalyst (moles)	Alkylated 2-furoic ester (yield)	Ref.
Methyl	*n*-propyl chloride	$AlCl_3$ (0.1–0.2)	5-*i*-propyl (48%)	109
Methyl	*i*-propyl chloride	$AlCl_3$ (0.1–0.2)	5-*i*-propyl (42%)	109
Methyl	*n*-butyl chloride	$AlCl_3$ (0.1–0.2)	5-*t*-butyl (45%)	109
Methyl	*i*-butyl bromide	$AlCl_3$ (0.1–0.2)	5-*t*-butyl (66%)	109
Methyl	*s*-butyl bromide	$AlCl_3$ (0.1–0.2)	5-*t*-butyl (2%)	109
Methyl	*t*-butyl bromide	$AlCl_3$ (0.1–0.2)	5-*t*-butyl (46%)	109
Methyl	*t*-butyl chloride	$FeCl_3$ (0.12)	5-*t*-butyl (41%)	109
Ethyl*	*t*-butyl chloride	HF	5-*t*-butyl (54%)	110
Methyl	*n*-pentyl chloride	$AlCl_3$ (0.1–0.2)	5-*t*-pentyl (31%)	109
Methyl	*t*-pentyl chloride	$AlCl_3$ (0.2)	5-*t*-pentyl (82%)	114
Methyl	*n*-hexyl bromide	$AlCl_3$ (0.1–0.2)	5-hexyl (57%)	109
Methyl	1-methylcyclohexyl chloride	$AlCl_3$ (0.2)	5-(1-methylcyclohexyl) (55%)	114

* Molar ratios of reactants and catalyst not given.

[114] Reichstein, Rosenberg and Eberhardt, *Helv. Chim. Acta*, **18**, 721 (1935).

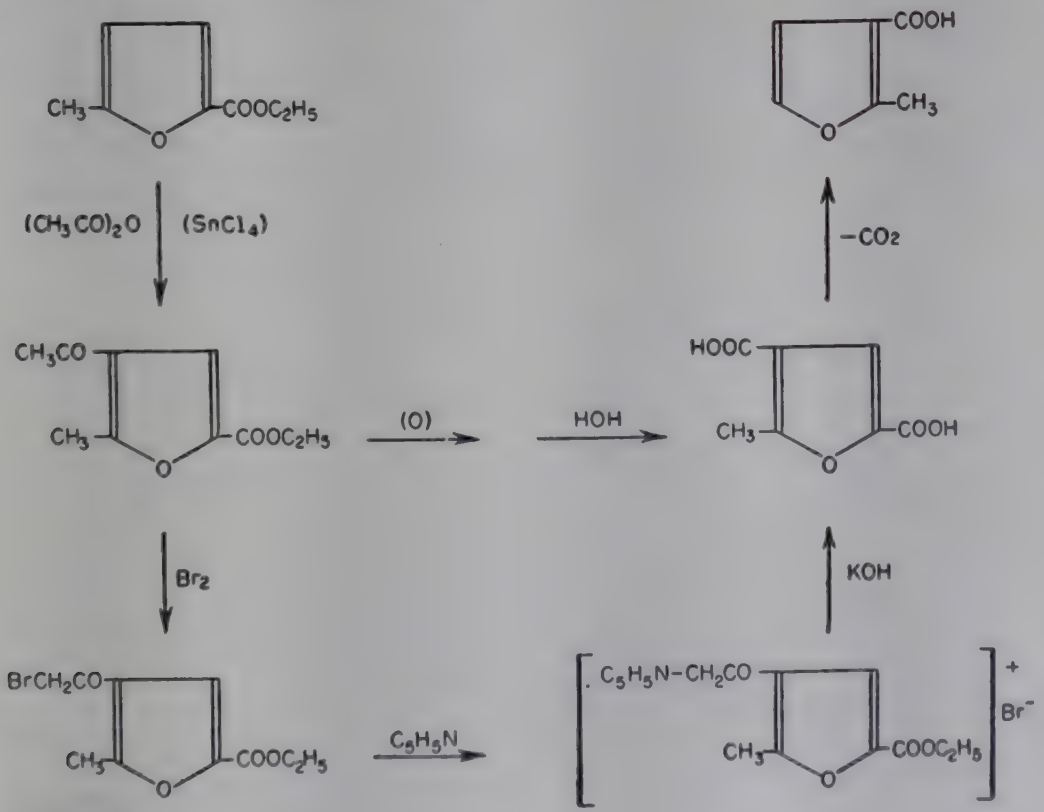
Quite surprisingly, aluminum chloride proved to be ineffective in promoting a Friedel-Crafts reaction of methyl 2-furoate with acetic anhydride or acetyl chloride, a result influenced, perhaps, by the quality of the condensing agent.[109] Acylation has been accomplished successfully, however, using acid anhydrides with either stannic or ferric chlorides. Substitution occurs in the 5-position, as shown by the isolation of 2-furyl methyl ketone by degradation of the keto ester obtained from ethyl 2-furoate and acetic anhydride.[109]

$$C_4H_3O{-}COOC_2H_5 \xrightarrow[(SnCl_4 \text{ or } FeCl_3)]{(CH_3CO)_2O}$$

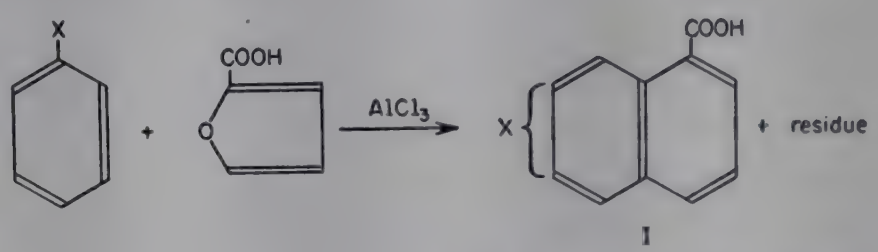
$$2,5\text{-}C_4H_2O{-}(COCH_3)(COOC_2H_5) \xrightarrow{HOH} \xrightarrow{-CO_2} C_4H_3O{-}COCH_3$$

In this acetylation reaction, the ease of alpha-substitution of a negatively substituted furan compound is strikingly illustrated by the fact that toluene may be employed as the solvent with the formation of little or no *p*-methylacetophenone.[115] By contrast, the di-α-substituted halofuroic ester, methyl 5-bromo-2-furoate, was recovered unchanged on similar treatment, reaction being confined to the solvent, toluene.[115]

Acetylation of ethyl 5-methyl-2-furoate resulted in the introduction of an acetyl group at the 4-position. The orientation was proven, as shown below, by conversion of the keto ester to the known 2-methyl-3-furoic acid by two separate procedures whereby the acetyl radical was oxidized to a carboxyl, (a) by permanganate oxidation, and (b) by way of the intermediate acylpyridinium bromide.[116]



Condensation with Aromatic Compounds Catalyzed by Aluminum Chloride. Aluminum chloride effects condensation of 2-furoic acid and its esters with aromatic compounds of the benzene and naphthalene series.[e] The reaction with benzene was first studied by King[118] who isolated a crystalline product, the structure of which was later established as 1-naphthoic acid by Gilman and his students.[119] The latter investigators demonstrated that toluene, anisole and chlorobenzene react in a similar manner with 2-furoic acid to give the corresponding substituted-1-naphthoic acids[120]; reaction with phenol was also successful, but failure was experienced in attempting to extend it to guaiacol, *o*-dimethoxybenzene (veratrole), pyrogallol and its trimethyl ether.[121] The product substituent was, in each instance, assigned to the 6-position, but recent work dealing with the condensation of chlorobenzene with methyl 2-furoate has revealed the formation of a mixture of 6- and 7-chloro-1-naphthoic acids, I.[122]

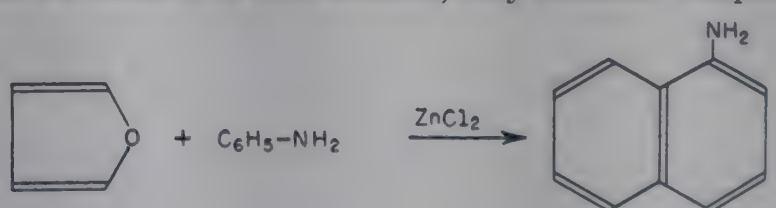


I

(X = H, CH_3, OH, OCH_3, or Cl)

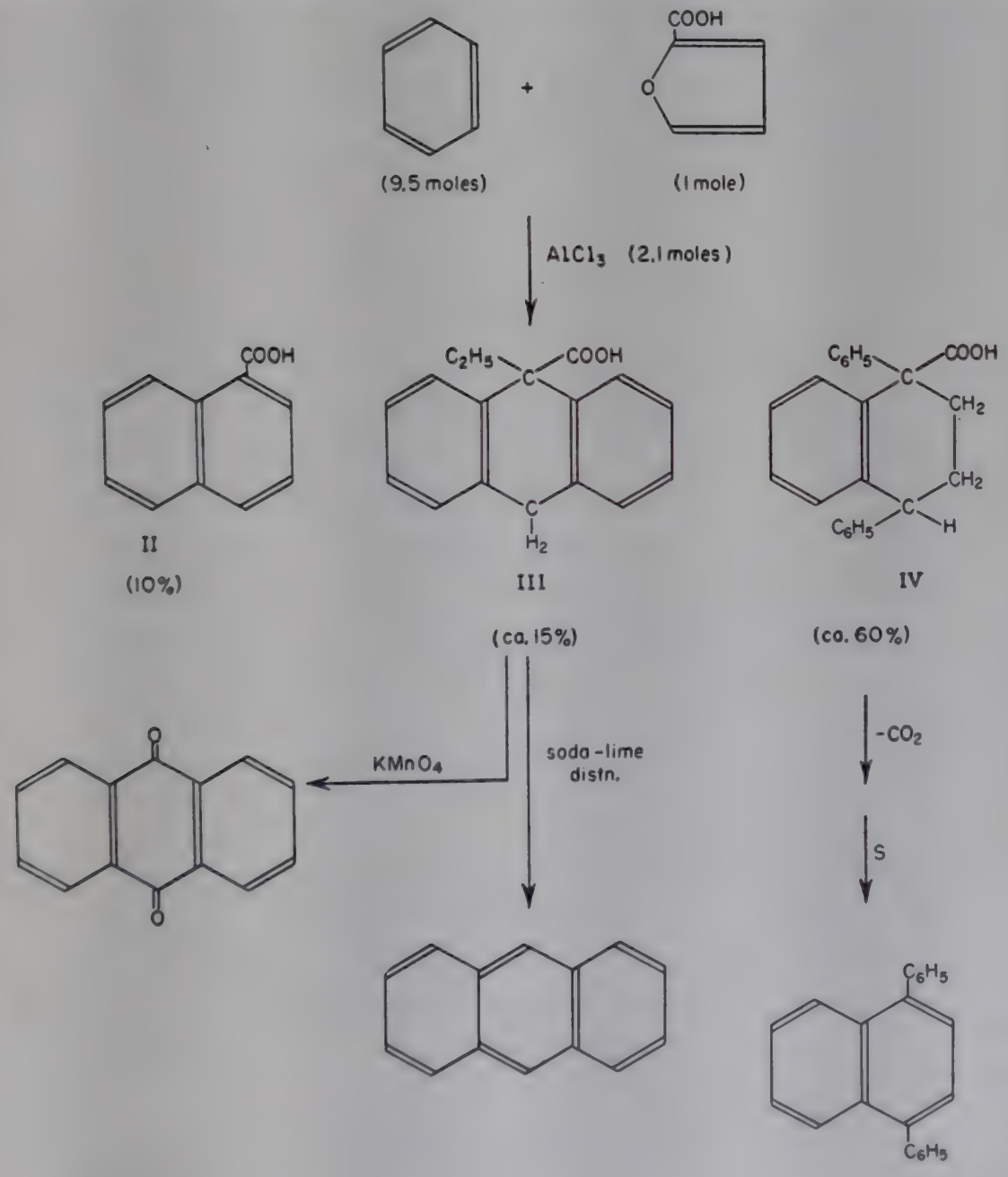
Price *et al.*[123, 124, 125] confirmed Gilman's findings, but called attention to the low yields (10–20 per cent) of the naphthoic acids which could be isolated in the pure state. From the reaction of 2-furoic acid with benzene, for example, Price isolated pure 1-naphthoic acid, II, in only ten per cent yield, and showed that the major products consisted of two higher molecular weight acids, obtained as an amorphous mixture which could not be

[e] Canzoneri and Oliveri[117] reported a related reaction between furan and aniline. On heating these materials with zinc chloride, they obtained 1-naphthylamine.



[115] Straley, *Iowa State Coll. J. Sci.*, **11**, 115 (1936).
[116] Gilman, Calloway and Smith, *J. Am. Chem. Soc.*, **56**, 220 (1934).
[117] Canzoneri and Oliveri, *Gazz. chim. ital.*, **16**, 476 (1886).
[118] King, *J. Am. Chem. Soc.*, **49**, 562 (1927).
[119] Gilman, McCorkle and Calloway, *J. Am. Chem. Soc.*, **56**, 745 (1934).
[120] McCorkle and Turck, *Proc. Iowa Acad. Sci.*, **43**, 205 (1936); *C. A.*, **32**, 4161 (1938).
[121] Haworth, Moore and Pauson, *J. Chem. Soc.*, **1949**, 3271.
[122] Jacobs *et al.*, *J. Org. Chem.*, **11**, 229 (1946).
[123] Price, Chapin, Goldman, Krebs and Shafer, *J. Am. Chem. Soc.*, **63**, 1857 (1941).
[124] Price and Huber, *J. Am. Chem. Soc.*, **64**, 2136 (1942).
[125] Price, Chapin and Rieger, *J. Am. Chem. Soc.*, **64**, 2227 (1942).

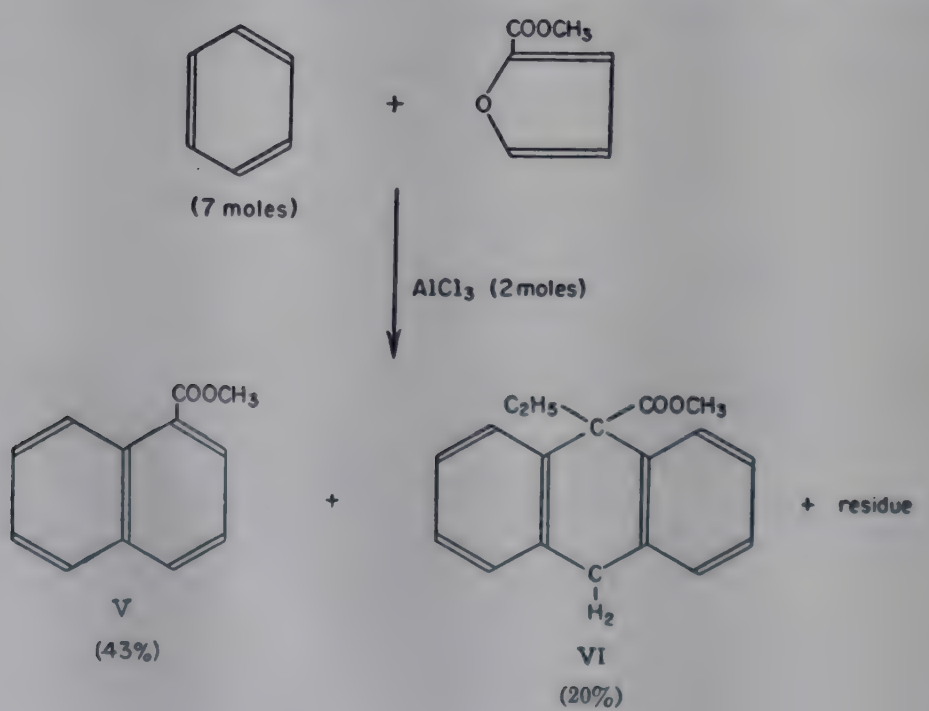
separated into its components by the usual methods. However, decarboxylation of the crude mixture yielded a neutral oil, which on dehydrogenation with sulfur gave 1,4-diphenylnaphthalene.[123] It was concluded that the precursor of this hydrocarbon was 1,4-diphenyl-1,2,3,4-tetrahydro-1-naphthoic acid, IV, formed by condensation of three molecules of benzene with one molecule of furoic acid with the elimination of one molecule of water. In lesser amount, the amorphous mixed acids contained an anthroic acid derived from two molecules of benzene and one molecule of furoic acid. This was deduced from the isolation of anthraquinone as a product of oxidation with alkaline permanganate[123] and anthracene as a degradation product on subjecting the crude mixture to distillation over soda lime.[125] It was suggested that the anthroic acid from which these products originated was 9,10-ethylene-9,10-dihydro-9-anthroic acid,[123] but on the basis of later work, Price assigned to it the structure of 9-ethyl-9,10-dihydro-



9-anthroic acid, III.[124, 125] Thus, reaction of benzene with 2-furoic acid yields at least three acidic products, as a result of the condensation of one, two and three molecules of benzene with one of furoic acid. It remains to be determined whether these products are formed simultaneously by separate routes, or stepwise whereby III and IV may have their origin in 1-naphthoic acid, II. In addition, it would be interesting to ascertain the effect, if any, of the temperature of condensation on the product yields.

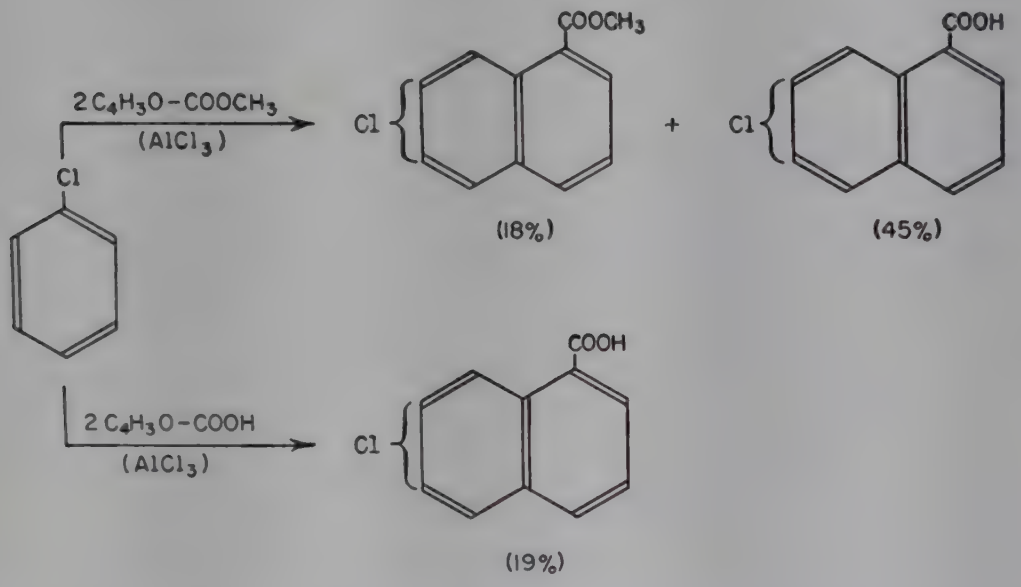
In addition to methyl- and methoxy-1-naphthoic acids, reaction of 2-furoic acid with toluene and anisole, respectively, likewise produced as the principal products, higher molecular weight acids resembling those from benzene. With chlorobenzene, on the other hand, the yield of high molecular weight acids was negligible, chloronaphthoic acid being isolated in somewhat better yield (19 per cent).[123]

Substitution of methyl 2-furoate for 2-furoic acid appears to favor equimolecular condensation at the expense of the reactions leading to higher molecular weight products. With aluminum chloride as catalyst, reaction of 2-furoic acid with benzene gave only ten per cent of 1-naphthoic acid, whereas methyl 1-naphthoate, V, was obtained in 43 per cent yield when the ester and benzene were condensed under more or less similar conditions.[124] In addition, methyl 9-ethyl-9,10-dihydro-9-anthroate, VI, was isolated in 20 per cent yield in the latter instance, compared to an estimated 15 per cent yield of the corresponding free acid from the reaction of furoic acid and benzene. It is indicated, therefore, that the termolecular condensation, that involving two molecules of benzene and one of furoic acid or its ester, proceeded to approximately the same extent in each instance; that the increase in yield of the 1:1 condensation product (V) when methyl furoate is employed in place of the free acid may be at the expense of the



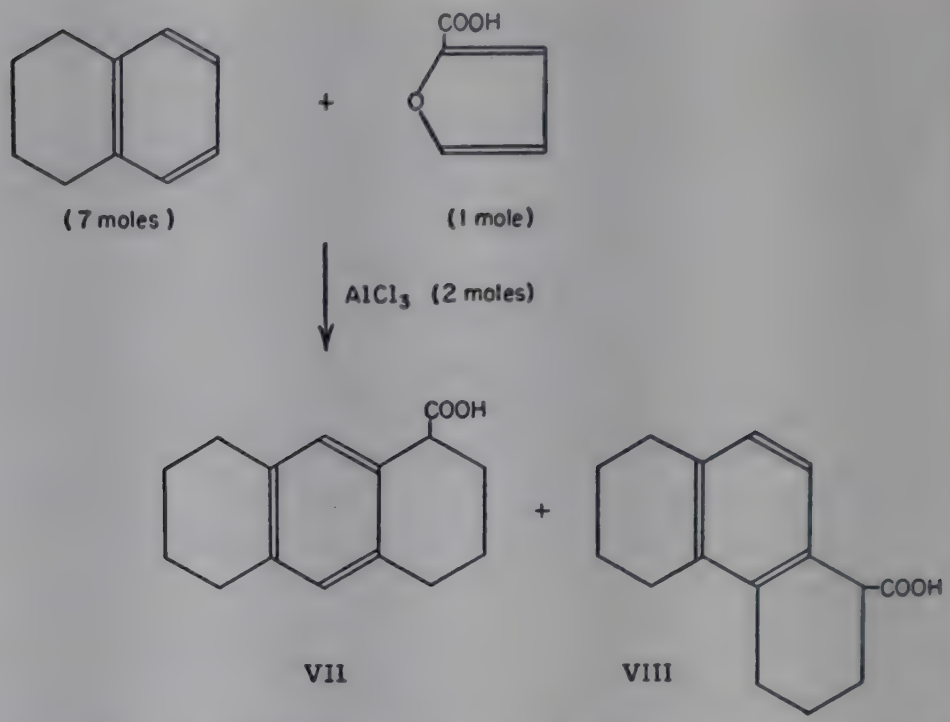
reaction in which three molecules of benzene condense with one molecule of the furan derivative.

Condensation of methyl furoate with chlorobenzene differed from the reaction illustrated above in that the ester group was largely cleaved to a free carboxyl group. What was believed to be pure 6-chloro-1-naphthoic acid was obtained in 45 per cent yield, and an additional 18 per cent of the initial furoic ester was accounted for as methyl chloronaphthoate.[124] Recently it has been demonstrated that the free acid fraction actually consisted of an eutectic mixture of the 6- and 7-chloro- acids.[122] No significant amount of high molecular weight products are formed, thereby checking the earlier experience in the reaction of chlorobenzene with 2-furoic acid.



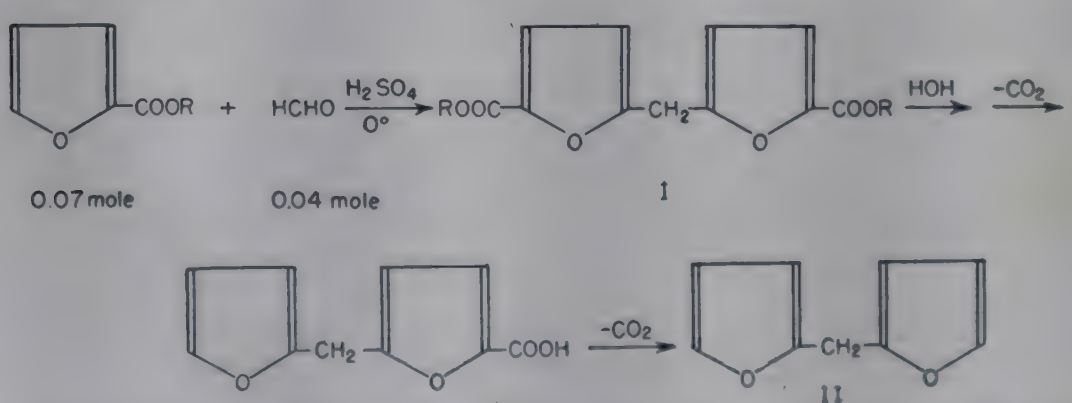
Price and Deno[126] extended the reaction and attempted condensation of furoic acid with naphthalene and with tetralin in the presence of aluminum chloride. The only product obtained in the former case was an amorphous, neutral black powder, but in the reaction with tetralin a considerable amount of material was obtained from which two isomeric, crystalline acids were isolated in low yield. It had been expected that the condensation with tetralin would produce tetrahydroanthroic or tetrahydrophenanthroic acids on the basis of the reactions of furoic acid with benzene and its derivatives. Analysis of the isolated acids, however, showed four more hydrogen atoms than called for by these structures, in all probability as a result of a disproportionation reaction involving the excess tetralin. The structures tentatively assigned to the products were *sym.*-octahydro-1-anthracenecarboxylic acid, VII, and *sym.*-octahydro-1-phenanthrenecarboxylic acid, VIII.

[126] Price and Deno, *J. Am. Chem. Soc.*, **64**, 2601 (1942).



Chloromethylation and Related Reactions. Under strongly acidic conditions, the hydrogen atom in the 5-position of 2-furoic acid or ester is sufficiently reactive to permit condensation with formaldehyde and other aldehydes. The simple 5-hydroxyalkyl-2-furoic acids have not been isolated in this way, although the corresponding chloroalkyl derivatives may be obtained in good yield by carrying out the reaction, under anhydrous conditions, in the presence of hydrogen chloride. Generally, condensation proceeds farther, depending upon reaction conditions (ratio of reactants, temperature, etc.) with the formation of binuclear products.

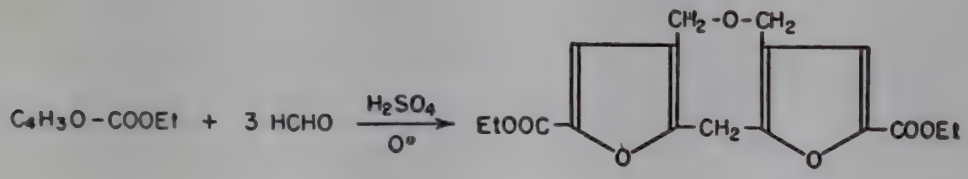
Dinelli and Marini[127, 128, 129] placed 2-furoic ester in reaction in concentrated sulfuric acid at 0° with several different aldehydes. With formaldehyde, actually paraformaldehyde, they were able to isolate alkyl 5-methylenedi-2-furoate, I,[f] in approximately 40 per cent yield. The structure was ascertained by conversion to the known 2,2′-difurylmethane, II, as indicated below. A similar result was obtained using acetaldehyde (as paralde-



[f] This ester and related carboxylic acids and esters of difuryl and its homologs are described later (p. 583).

hyde) which gave alkyl 5-ethylidenedi-2-furoate. Yields up to 90 per cent were obtained under carefully controlled conditions, demonstrating the high degree of nuclear stability of furoic ester. With benzaldehyde only a trace of crystalline material, m.p. 212°, could be isolated, but its analysis corresponded to alkyl 5-benzylidenedi-2-furoate.

In reactions of this type a considerable portion of the product is resinous, the amount of which is greatly increased when an excess of aldehyde is employed. More complex condensation products are formed under these circumstances, with the indication that the hydrogen atoms in the beta as well as the alpha positions of the furan nucleus are involved in the reaction. Thus, from the resinous mass obtained by condensation of ethyl 2-furoate with approximately four times the amount of formaldehyde indicated above, Dinelli and Marini[128] isolated a crystalline compound ($C_{17}H_{18}O_7$) melting at 192°. Tests for alcohol and carboxyl groups gave negative results. Hydrolysis yielded an acid, $C_{13}H_{10}O_7$ (did not fuse up to 280°) which on decarboxylation gave a compound, $C_{11}H_{10}O_3$, melting at 128°. The latter took up four moles of hydrogen over platinum oxide catalyst with the formation of $C_{11}H_{18}O_3$, b.p. 150° (4 mm.). It was concluded that the original compound was the internal ether, III, of alkyl 5-methylenebis(4-hydroxymethyl-2-furoate).



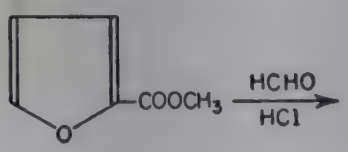
III

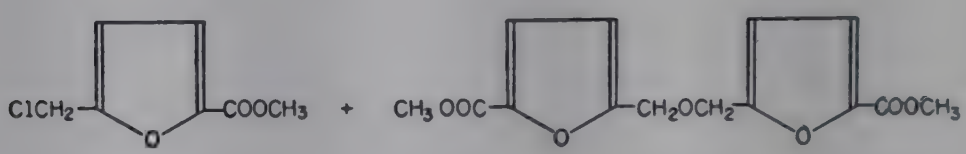
On the basis of these syntheses of difurylmethane derivatives, it occurred to Dinelli and Marini that condensation of furoic ester with furaldehydes would give derivatives of trifurylmethane which might be useful as dyestuffs. In view of the necessity of conducting the reaction in strongly acidic medium, they selected 5-nitrofurfural rather than furfural. Reaction of the nitrofurfural with ethyl furoate was carried out at room temperature in concentrated sulfuric acid. Oxides of nitrogen were evolved indicating loss of the nitro group, and from the reaction mixture two products were isolated which await definite characterization. Both were found to be devoid of nitrogen; red (m.p. 125°) and blue (m.p. 215°) crystalline products, the former having the empirical constitution $C_{19}H_{16}O_8$. Both, on saponification, gave sodium salts which acted like true dyes on wool and silk.

The preparation of 5-chloromethyl-2-furoic esters is described in a pat-

[127] Dinelli and Marini, *Gazz. chim. ital.*, **67**, 312 (1937); *C. A.*, **32**, 154 (1938)
[128] Dinelli and Marini, *Gazz. chim. ital.*, **67**, 417 (1937); *C. A.*, **32**, 1261 (1938).
[129] Dinelli and Marini-Bettolo, *Gazz. chim. ital.*, **71**, 117 (1941); *C. A.*, **36**, 1928 (1942).

ented disclosure by Bremner and Jones[130] (see also [131]). Thus, treatment of a mixture of methyl furoate, paraformaldehyde and zinc chloride, in a chlorinated hydrocarbon solvent, with dry hydrogen chloride at 30–35° for one hour gave the 5-chloromethyl ester, IV (p. 557), in 60 per cent yield. A by-product of the reaction was methyl 5-(oxydimethylene)di-2-





IV V

furoate, V. Other dehydrating agents may be substituted for the zinc chloride, phosphoric acid being particularly effective. Among other things, the use of a solvent facilitates control of the temperature, which should be maintained below 30° for optimum yields. Higher temperatures are less desirable because of their effect in promoting the formation of binuclear products. Thus, when the above condensation was conducted at 70° in the absence of a solvent, the major product was found to be methyl 5-methylenedi-2-furoate, $(CH_3OOC—C{=}CH—CH{=}C—)_2CH_2$.



Direct aminomethylation of furoic acid or ester, as by reaction with formaldehyde and an amine has not been reported. However, in the presence of concentrated sulfuric acid, condensation with N-hydroxymethylamides leads to the formation of 5-(acylaminomethyl)-2-furoic acids, VI.

$$C_4H_3O—COOH + RCONH(CH_2OH) \rightarrow 2,5\text{-}C_4H_2O—(CH_2NHCOR)(COOH)$$

VI

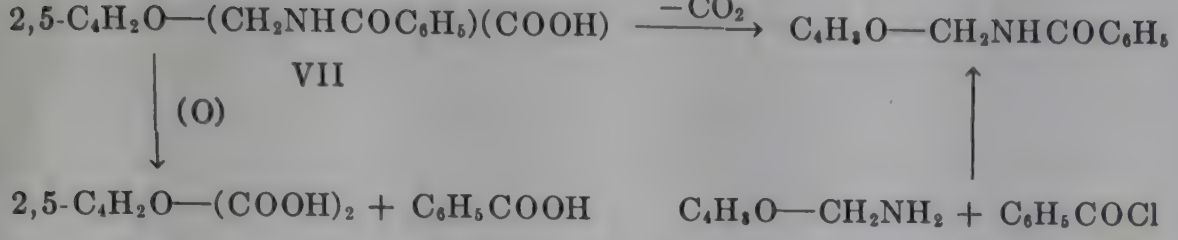
Marini[132] and Cinneide[133] synthesized several compounds of this general type (p. 557), the yields being in the neighborhood of 40 per cent. The structure of 5-(benzamidomethyl)-2-furoic acid, VII, was proved by the transformations shown below.[133]

[130] Bremner, Jones and Imperial Chemical Industries Ltd., British Patent 588,377 (1947); *C. A.*, **41**, 6581 (1947).

[131] Bremner and Jones (to Imperial Chemical Industries Ltd.), U. S. Patent 2,450,108 (1948); *C. A.*, **43**, 1065 (1949).

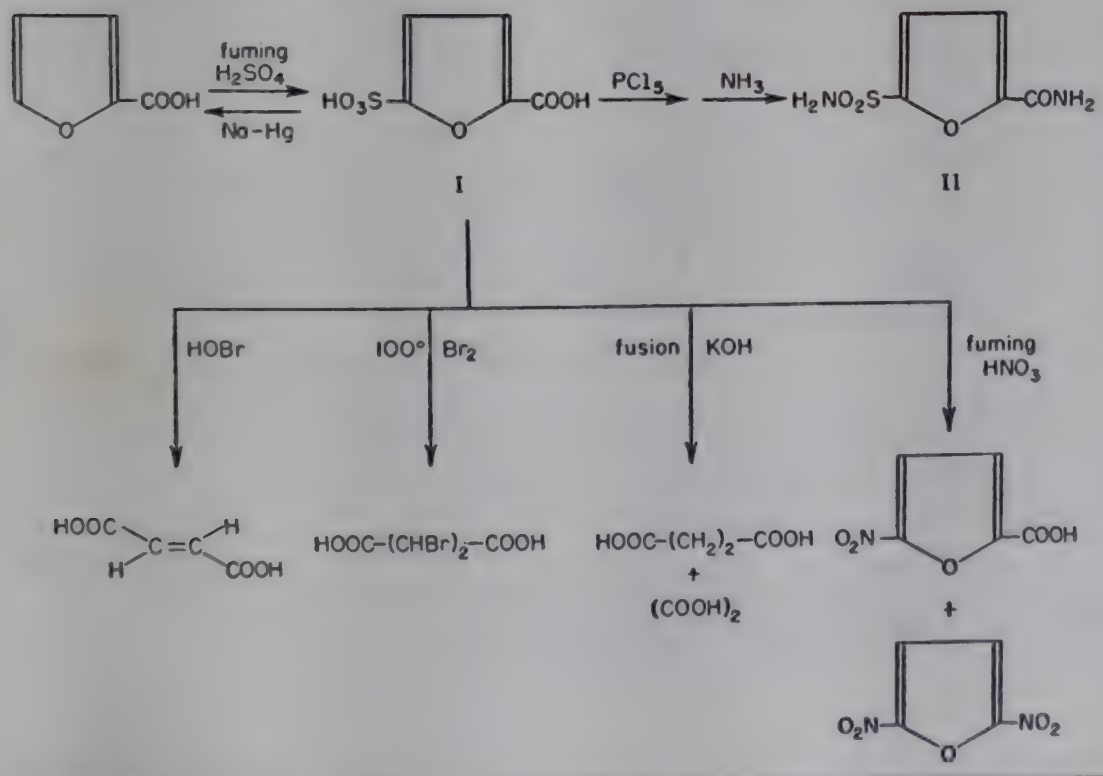
[132] Marini, *Gazz. chim. ital.*, **69**, 340 (1939); *C. A.*, **33**, 8607 (1939).

[133] Cinneide, *Proc. Roy. Irish Acad.*, **49**, **B**, 143 (1943).



Sulfonation. The introduction of a sulfonic acid group into 2-furoic acid[a] is readily achieved by slow addition of the latter to fuming sulfuric acid. In this way, 5-sulfo-2-furoic acid, I (no physical constants reported), was isolated in the form of the barium salt ($BaC_5H_2SO_6$; sol. in H_2O = 3.41 per cent at 21°). The reaction was first carried out by Schwanert,[28] but our knowledge of the product is due, primarily, to Hill and Palmer.[134, 135, 136] The milder sulfonating agent, 1-proto-1-pyridinesulfonate, which has been employed so successfully for introducing a sulfo group into furan and its homologs, fails to react with furoic acid (in chlorobenzene) below 135°, and under these conditions, decarboxylation takes place and 2-furansulfonic acid is obtained (see p. 72).

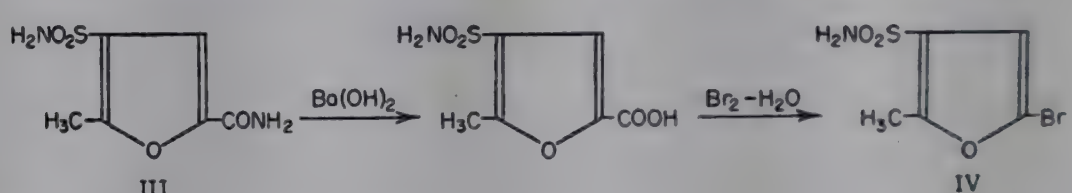
Treatment of I with phosphorus pentachloride and then with aqueous ammonia results in the formation of 5-sulfamido-2-furamide, II (m.p. 213°)[134, 135, 136] (see also [137]). At room temperature, dry bromine has little effect on I; at 100°, dibromosuccinic acid is obtained as the major product. Treatment with aqueous bromine produces fumaric acid. Fusion with potassium hydroxide gives succinic and oxalic acids. With fuming nitric acid, the sulfo group, and to a lesser extent the carboxyl, is replaced by $—NO_2$.[134, 135, 136] Removal of the sulfo group is also achieved by reduction with sodium amalgam, a result which is not realized when the sulfo group is attached to a β-nuclear carbon atom.[138]



[a] The sulfonation of halogen substituted furoic acids is discussed in Chapter 3.

The alpha location of the sulfo group is known, (1) by the loss of this group on oxidation with aqueous bromine (see p. 128), and (2) by formation of the same sulfofuroic acid following removal of the halogen atoms from sulfo-3,4-dihalo-2-furoic acid.[138] The isomeric 4-sulfo-2-furoic acid (barium salt, $BaC_5H_2SO_6$; sol. in H_2O = 1.91 per cent at 21°) is obtained by sulfonating 5-halo-2-furoic acid and reducing the sulfo-halo acid with zinc dust in ammoniacal solution.[138] With aqueous bromine, it is oxidized to sulfofumaric acid.[139] The third position-isomer, 3-sulfo-2-furoic acid, has not yet been reported.

Sulfonation of 5-methyl-2-furoic acid with fuming sulfuric acid introduces one sulfo group; most probably in the 4-position. The resulting β-sulfomethylfuroic acid, isolated as the barium salt,[29] was converted into the dichloride (not isolated) with phosphorus pentachloride, and thence to the diamide, III (m.p. 196–197°).[140] III with barium hydroxide lost ammonia to give β-sulfamido-5-methyl-2-furoic acid (m.p. 217–218°), which on careful treatment with one mole of bromine in aqueous alkali gave rise to β-sulfamido-5-methyl-2-bromofuran, IV (m.p. 123°).[140]



III IV

Functional Derivatives of 2-Furoic Acid

Esters. Esters of 2-furoic acid are obtained by standard procedures with no special precautions. Direct esterification of the acid by alcohols is achieved with hydrogen chloride or sulfuric acid as condensing agents. The action of 2-furoyl chloride on hydroxylic compounds likewise gives rise to the esters in the normal manner. Furfuryl 2-furoate, however, calls for special comment.

Furfuryl 2-furoate: Direct esterification with furfuryl alcohol is impractical because of its sensitivity to acids. The use of furoic anhydride with the alcohol likewise leads to rather extensive resinification of the latter. For this reason, Zanetti[141] resorted to the Schotten-Baumann procedure, adding 2-furoyl chloride slowly to a cold, aqueous, alkaline solution of furfuryl alcohol.

An improved procedure for this synthesis has been reported by Nielsen.[142] This

[134] Hill and Palmer, *Ber.*, **18**, 2095 (1885).
[135] Hill and Palmer, *Proc. Am. Acad. Arts Sci.*, **23**, 188 (1887).
[136] Hill and Palmer, *Am. Chem. J.*, **10**, 373 (1888).
[137] Cinneide, *Nature*, **160**, 260 (1947).
[138] Hill and Hendrickson, *Am. Chem. J.*, **15**, 145 (1893).
[139] Hill and Palmer, *Am. Chem. J.*, **10**, 409 (1888).
[140] Hill and Sylvester, *Am. Chem. J.*, **32**, 185 (1904).
[141] Zanetti, *J. Am. Chem. Soc.*, **47**, 1452 (1925).
[142] Nielsen, *J. Am. Chem. Soc.*, **66**, 1230 (1944).

involves a modified Tischenko reaction whereby furfural is dimerized under the influence of sodium furfuroxide. Although an earlier attempt to use this method had been unsuccessful,[141] Nielsen was able to isolate the pure ester in 78 per cent yield.

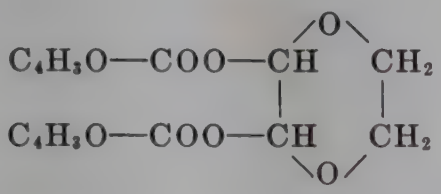
$$C_4H_3O{-}COCl + C_4H_3O{-}CH_2OH \xrightarrow{KOH} \rightarrow$$

$$2\ C_4H_3O{-}CHO \xrightarrow{C_4H_3O{-}CH_2ONa} \rightarrow$$

$$C_4H_3O{-}COOCH_2{-}C_4H_3O$$

Furfuryl 2-furoate is a water-white, viscous liquid which boils above 350° at atmospheric pressure with much decomposition; b.p. 122° (2 mm.); d_{25}^{25} 1.2384; n_D^{20} 1.5280. Zanetti[141] (see also [143]) found the ester to exist in two forms, one melting at 19.5° and the other at 27.5°. He noted that, on standing, crystals of the former type passed into the allotropic, higher-melting form. Contrary to this observation is the fact that Nielsen's[142] product melted at 18.5° (uncorr.) and failed to undergo any similar transformation on standing.

2,3-Dioxanediol di-2-furoate:



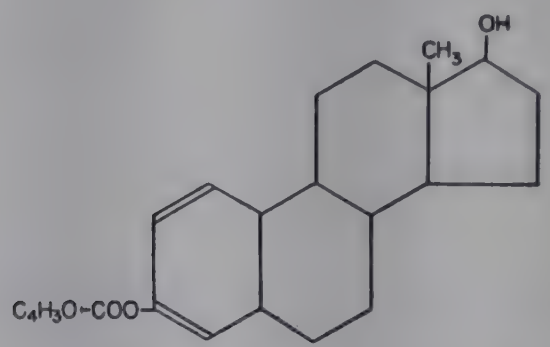
m.p. 73°, b.p. 174–183° (6–7 mm.); by heating 2,3-dichloro-*p*-dioxane and 2-furoic acid in an aromatic hydrocarbon.[178]

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[143] Zanetti and Kerr, *J. Am. Chem. Soc.*, **48**, 794 (1926).
[144] Gennari, *Gazz. chim. ital.*, **24, I**, 246 (1894).
[145] Rogerson, *J. Chem. Soc.*, **101**, 1040 (1912).
[146] Sunier, *J. Phys. Chem.*, **35**, 1756 (1931).
[147] Vernon, Struss and Ruwe, *Trans. Kentucky Acad. Sci.*, **9**, 23 (1941); *C. A.*, **36**, 4504 (1942).
[148] Guainazzi, *Pitture e vernici*, **4**, 181 (1948); *C. A.*, **43**, 4252 (1949).
[149] Trickey, *Ind. Eng. Chem.*, **19**, 643 (1927).
[150] Trautner and Polya, *Australian Chem. Inst. J. and Proc.*, **15**, 52 (1948); *C. A.*, **42**, 5848 (1948).
[151] Malaguti, *Ann. chim. phys.* (*2*), **64**, 275 (1837).
[152] Curtius and Leimbach, *J. prakt. Chem.*, **65**, 20 (1902).
[153] Marquis, *Ann. chim. phys.* (*8*), **4**, 196 (1905).
[154] Kotake and Fujita, *Bull. Inst. Phys.-Chem. Res. Tokyo, Abstracts of*, **I, 7**, 65 (1928).
[155] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).
[156] Kindler, *Ber.*, **69**, 2792 (1936).
[157] Zellhoefer, Copley and Marvel, *J. Am. Chem. Soc.*, **60**, 1337 (1938).
[158] Gilman and Yale, *J. Am. Chem. Soc.*, **72**, 3593 (1950).
[159] Gilman, Heckert, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **7**, 419 (1933).
[160] Hester, (to Röhm and Haas Co.), U. S. Patent 2,220,521 (1940); *C. A.*, **35**, 1906 (1941).
[161] Burtner and Lehmann, *J. Pharmacol. Exptl. Therap.*, **63**, 183 (1938).
[162] Zanetti and Beckmann, *J. Am. Chem. Soc.*, **48**, 1067 (1926).
[163] Hammer, *Chemistry and Industry*, **1933**, 608.

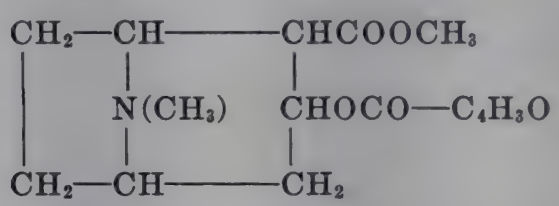
Di-2-furoyltartaric dialkyl ester: $C_4H_3O—CO(CHCOOR)_2OCO—C_4H_3O$; m.p. 131° (R = CH_3); m.p. 76° (R = C_2H_5); by the action of 2-furoyl chloride on tartaric ester.[165]

Estradiol 3-(2-furoate):



m.p. 195°; from 2-furoyl chloride and estradiol. Ratio of estrogenic activity to that of estradiol monobenzoate is 1.4/1.[179]

(2-Furoyl)ecgonine methyl ester:



m.p. 142–143°; **hydrochloride,** m.p. 184.5°; **picrate,** m.p. 167–169°; **chloroplatinate,** m.p. 231° (dec.). This product, the furan analog of cocaine, was obtained by furoylating ecgonine methyl ester with 2-furoic anhydride.[180]

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[164] Holdren and Barry, *J. Am. Chem. Soc.*, **69,** 1230 (1947).

[164a] Nakai, *Biochem. Z.*, **152,** 258 (1924); *C. A.*, **19,** 2807 (1925).

[165] Mangini, *Bull. soc. chim. Belg.*, **1940,** 167; *C. A.*, **36,** 5812 (1942).

[166] Slagh, (to Dow Chemical Co.), U. S. Patent 2,195,382 (1940); *C. A.*, **34,** 5092 (1940).

[167] Coleman and Hadler, (to Dow Chemical Co.), U. S. Patent 2,127,660 (1938); *C. A.*, **32,** 7925 (1938).

[168] Gilman and Pickens, *J. Am. Chem. Soc.*, **47,** 245 (1925).

[169] Lyons and Reid, *J. Am. Chem. Soc.*, **39,** 1727 (1917).

[170] Baum, *Ber.*, **37,** 2949 (1904).

[171] Gilman and Dickey, *Rec. trav. chim.*, **52,** 389 (1933).

[172] Raiford and Huey, *J. Org. Chem.*, **6,** 858 (1941).

[173] Hiemenz and Freedman, (to Bayer Co.), U. S. Patent 2,140,052 (1939); *C. A.*, **33,** 2286 (1939).

[174] Hiemenz and Freedman, (to I. G. Farbenind. Akt.-Ges.), German Patent 704,909 (1941); *C. A.*, **36,** 2086 (1942).

[175] I. G. Farbenind. A.-G., French Patent 826,344 (1938); *C. A.*, **32,** 7478 (1938).

[176] Kleene, *J. Am. Chem. Soc.*, **68,** 718 (1946).

[177] Judefind and Reid, *J. Am. Chem. Soc.*, **42,** 1043 (1920).

[177a] Kipnis, Soloway and Ornfelt, *J. Am. Chem. Soc.*, **71,** 10 (1949).

[178] Slagh, (to Dow Chemical Co.), U. S. Patent 2,164,355 (1939); *C. A.*, **33,** 8210 (1939).

[179] Morren, *J. Pharm. Belg.*, **23,** 56 (1941); *C. A.*, **38,** 2046 (1944).

[180] Katsnel'son and Gol'dfarb, *Compt. rend. acad. sci. U.R.S.S., N. S.*, **4,** 413 (1936). *C. A.*, **31,** 3491 (1937).

TABLE 4. SOME 2-FUROIC ESTERS

2-Furoic ester	Physical constants (°C.)	Ref.
Methyl	b.p. 181; 83–84 (25 mm.) $d_4^{21.4}$ 1.1786; d_{15}^{15} 1.1739 $n_D^{21.4}$ 1.4871; n_D^{20} 1.4860	144, 145, 146, 148, 149, 150
Ethyl	m.p. 32–33, 34 b.p. 128 (95 mm.), 193–195 $d_4^{20.8}$ 1.1174; d_4^{40} 1.0974 $n_D^{20.8}$ 1.4797	151, 101, 144, 152, 153, 146, 154, 155, 156, 147, 148, 157, 149
2-Hydroxyethyl	m.p. 63–65; b.p. 161–162 (15 mm.)	158
2-Chloroethyl	b.p. 116–117 (9 mm.), 155 (30 mm.) d 1.2952	159, 160
2,2,2-Trichloroethyl	b.p. 145–147 (15 mm.)	161
2,2,2-Tribromoethyl	b.p. 149–153 (10 mm.)	161
2-Thiocyanoethyl	—	160
Propyl, *n*-	b.p. 211; 105–107 (25 mm.) $d_4^{25.6}$ 1.0745; $n_D^{25.9}$ 1.4737	144, 146, 149
i-	b.p. 198–199 $d_4^{23.7}$ 1.0655; $n_D^{23.7}$ 1.4682	144
2-Hydroxypropyl	—	158
3-Chloro-2-hydroxypropyl	b.p. 191 (15 mm.); n_D^{20} 1.5191	158
Trichloro-*i*-propyl	b.p. 150–152 (25 mm.)	161
Butyl, *n*-	b.p. 83–84 (1 mm.), 118–120 (25 mm.) d_4^{20} 1.0555	162, 146, 163, 149
sec-	b.p. 67–69 (1 mm.); d_4^{20} 1.0465	162
i-	b.p. 221–223 $d_4^{27.5}$ 1.0383; $n_D^{27.5}$ 1.4676	144
t-	b.p. 90 (24 mm.)	164
Pentyl, *n*-	b.p. 95–97 (1 mm.); d_4^{20} 1.0335	162

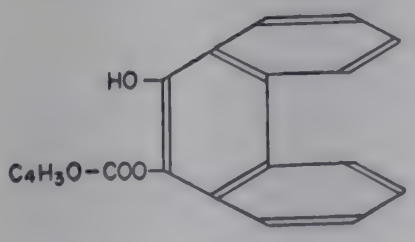
TABLE 4.—*Continued*

2-Furoic ester	Physical constants (°C.)	Ref.
i-	b.p. 111–111.5 (11 mm.); n_D^{20} 1.4724; d_4^{20} 1.030	41, 164a
sec-	b.p. 75–77 (1 mm.); d_4^{20} 1.039	162
hexyl, *n*-	b.p. 105–107 (1 mm.); d_4^{20} 1.0170	162
sec-	b.p. 86–88 (1 mm.); d_4^{20} 1.012	162
n-Heptyl	b.p. 116–117 (1 mm.); d_4^{20} 1.0005	162
n-Octyl	b.p. 126–127 (1 mm.); d_4^{20} 0.9885	162
Allyl	b.p. 206–209, 81–82 (4–5 mm.) d_{25}^{25} 1.118; n_D^{20} 1.4945	165, 166
Methallyl	b.p. 82–84 (2.5 mm.) d_{25}^{25} 1.086; n_D^{25} 1.4922	166
2-Chloroallyl	b.p. 105–107 (4 mm.) d_4^{20} 1.253; n_D^{20} 1.530	167
3,7-Dimethyl-2,6-octadienyl (from geraniol)	b.p. 148–155 (5 mm.); d_{25}^{25} 0.975	166
Cyclohexyl	b.p. 122–124 (2 mm.); m.p. 32–33	164
Benzyl	b.p. 141–142 (2 mm.), 179–181 (18 mm.) d_4^{20} 1.1632; n_D^{20} 1.5550	168, 164
p-Nitrobenzyl	m.p. 133.5	169
Phenyl	m.p. 42; b.p. 138–139 (3 mm.)	170, 171, 159
m-Cresyl	m.p. 39.5; b.p. 155 (5 mm.)	159
p-Cresyl	m.p. 55; b.p. 152 (5 mm.)	159
o-Methoxyphenyl	m.p. 76; b.p. 175 (5 mm.)	159
o-Nitrophenyl	m.p. 83–84	172
o-Carboxyphenyl (furoylsalicylic acid)	m.p. 131–132	173, 174, 175

TABLE 4.—*Continued*

2-Furoic ester	Physical constants (°C.)	Ref.
o-(2-Furamido)phenyl	m.p. 113–114	172
o-(2-Furoyloxy)phenyl (catechol difuroate)	m.p. 116	159
m-(2-Furoyloxy)phenyl (resorcinol difuroate)	m.p. 128–129, 130	170, 159
p-Hydroxyphenyl (hydroquinone monofuroate)	m.p. 193–195	171, 159
p-(2-Furoyloxy)phenyl (hydroquinone difuroate)	m.p. 200	171, 159
p-(2-Furoyl)phenyl (*p*-furoyloxyphenyl furyl ketone)	m.p. 84	171
2-Nitro-4-bromophenyl	m.p. 88–89	172
2-Nitro-4,6-dibromophenyl	m.p. 133–134	172
2-Nitro-4-bromo-5-methylphenyl	m.p. 74–76	172
Phenacyl	m.p. 85–86	176
p-Phenylphenacyl	m.p. 110–111	176
p-Bromophenacyl	m.p. 138.5	177
Thenacyl	m.p. 93.5	177a
2-Naphthyl	m.p. 121–122	115

9,10-Phenanthrenediol mono-2-furoate (phenanthrene-hydroquinone mono-2-furoate):

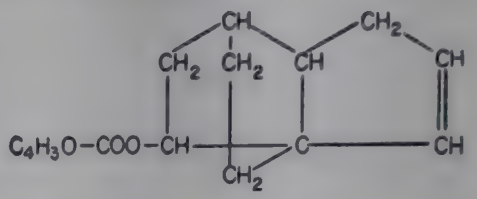


m.p. 193°; crystallizes from glacial acetic acid in tetragonal columns.[181, 182] The ester

[181] Johnsen, *Neues Jahrb. Min. Geol., etc.*, **1907, I,** 89; *C. A.*, **1,** 2075 (1907).

was obtained from a mixture of 9,10-phenanthraquinone and furfural in benzene which was exposed to sunlight for 53 days.[183]

Dihydronordicyclopentadienyl 2-furoate:



m.p. 72°, 73°; b.p. 165–167° (2 mm.). Prepared from dicyclopentadiene and 2-furoic acid using boron fluoride etherate catalyst. The dicyclopentadiene rearranges and adds the acid across one double bond; even in presence of excess of the acid, the remaining double bond is unaffected. Esters of this type are reported to be useful as plasticizers for synthetic resins and natural and synthetic rubber[184] (see also [185]).

Sucrose octa-2-furoate: Sinters at 88°; melts gradually from 90–99°; $[\alpha]_D^{25}$ +48.2 in $CHCl_3$; from sucrose and furoyl chloride in pyridine.[185a]

Cellulose di- and tri-2-furoate: Prepared from cellulose and 2-furoyl chloride by a modified Schotten-Baumann procedure. Fibrous, dark colored products, insoluble in the usual solvents for cellulose esters[186] (see also [26]).

Bornyl and fenchyl 2-furoates: Prepared from borneol and from fenchyl alcohol and furoic acid, and investigated as plasticizers for cellulose derivatives.[187]

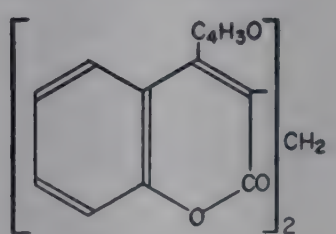
Bornyl 2-furoate, b.p. 275°.

Fenchyl 2-furoate, b.p. 275°; n_D 1.5019.

Difuroylhexestrol: m.p. 177–178°; from furoyl chloride and hexestrol in pyridine.

Difuroyldienestrol: m.p. 181–182°; in similar manner from dienestrol. It is reported that furoylated derivatives of estrogenic compounds exhibit greater estrogenic activity than the corresponding benzoyl derivatives.[188]

3,3′-Methylenebis-4-hydroxycoumarin di-2-furoate:



m.p. 298–300°.[189]

The esters of 2-furoic acid are stable compounds, although they tend to

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[182] Groth, "Chemische Krystallographie", Vol. 5, p. 498, Leipzig, w. Engelmann (1906–1919).

[183] Klinger, *Ann.*, **382,** 211 (1911); **249,** 137 (1888).

[184] Bruson, (to Resinous Products and Chemicals Co.), U. S. Patent 2,395,452 (1946); *C. A.*, **40,** 3138 (1946).

[185] Bruson and Riener, *J. Am. Chem. Soc.*, **67,** 1178 (1945).

[185a] Zief, *J. Am. Chem. Soc.*, **72,** 1137 (1950).

[186] Kobe and Montonna, *J. Am. Chem. Soc.*, **53,** 1889 (1931).

[187] Borglin, *Ind. Eng. Chem.*, **28,** 31 (1936).

[188] Colonna, *Boll. sci. facoltà chim. ind. univ. Bologna*, **6,** 38 (1948); *C. A.*, **44,** 1941 (1950).

[189] Stahmann, Graf, Huebner, Roseman and Link, *J. Am. Chem. Soc.*, **66,** 900 (1944).

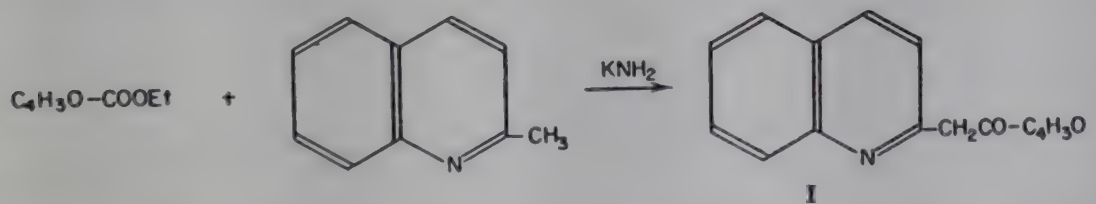
discolor on standing in air. This is due to absorption of oxygen, and may be avoided by storage under a blanket of inert gas. Under these conditions, the esters may be stored indefinitely with little or no deterioration.

The alkyl 2-furoates are colorless liquids of pleasant odor. Only the ethyl ester (m.p. 32–33°) is a solid at or near room temperature. They are quite resistant to hydrolysis in neutral medium, and may be steam distilled without undue loss. The boiling points of the *n*-alkyl esters at 1 mm. show a regular increase of approximately 10° between homologs, and a similar trend (from 8 to 11°) is noted between homologous *sec*-alkyl 2-furoates.[162]

In general, the esters are insoluble or only slightly soluble in water, but very soluble in alcohol and ether. Sunier[146] determined the solubility of naphthalene in several alkyl 2-furoates in connection with his investigation of the relationship between polarity and solubility. He observed a regular increase in solvent power as the size of the alkyl group increased from methyl to *n*-butyl. Furfuryl alcohol was found to be a much poorer solvent for naphthalene than any of these esters. Furfuryl acetate gave a solubility curve closely duplicating that obtained using methyl 2-furoate.[146] The properties of aqueous monomolecular films of hexadecyl 2-furoate [also hexadecyl 3-(2-furyl)acrylate and furfuryl palmitate] were studied by Tatiiri[190] who measured the surface pressure-area relationships obtaining in such systems.

The esters derived from unsaturated alcohols, allyl 2-furoate and related compounds possessing one or more —CH=CH-groups in the side chain, are reported to be useful as modifying agents in the polymerization of vinyl compounds, particularly styrene.[166] The allyl ester polymerizes on the application of heat to a brown, glassy resin.[165]

Quinaldine condenses with ethyl 2-furoate in the presence of potassium amide to give β-(2-furoylmethyl)quinoline, I, in 28 per cent yield.[191] Simi-



I

larly, under the influence of appropriate reagents, furoic ester condenses with compounds possessing a —CH_2— group which is activated by an adjacent carbonyl group. Thus, ethyl 2-furoylacetate is obtained from ethyl furoate and ethyl acetate[192, 193]; and the expected 1,3-diketones are

[190] Tatiiri, *J. Chem. Soc. Japan*, **60**, 442 (1939); *C. A.*, **35**, 5091 (1941).
[191] Bergstrom and Moffat, *J. Am. Chem. Soc.*, **59**, 1494 (1937).
[192] Bouveault, *Bull. soc. chim.* (*3*), **25**, 435 (1901).
[193] Ciusa, *Gazz. chim. ital.*, **52**, II, 43 (1922); *C. A.*, **17**, 1478 (1923).

formed when furoic ester is treated with methyl ketones using sodium,[194] sodium ethoxide,[195, 196, 197] or sodium amide[198] as condensing agents.

$$C_4H_3O\text{—}COOEt + CH_3COR \xrightarrow{NaOEt} C_4H_3O\text{—}COCH_2COR$$

Alternatively, the same products have been obtained by an acyl exchange reaction in which the furoyl radical of ethyl furoate replaces the acetyl group of a 1,3-diketone or β-keto-ester of the type CH_3COCH_2COR where R is CH_3 or C_6H_5 (see p. 440), or OC_2H_5 (see p. 602).[199]

The redistribution of radicals occurring when ethyl furoate is refluxed with an equimolecular quantity of furfuryl acetate in the presence of a small amount of aluminum ethoxide was investigated by Calingaert *et al.*[200] Examination of the boiling point curve of the reaction mixture showed that the anticipated exchange reaction had taken place; that all four of the possible products were present, (1) ethyl acetate, (2) furfuryl acetate, (3) ethyl furoate, and (4) furfuryl furoate.

The action of organomagnesium halides on 2-furoic ester was studied by Hale, McNally and Pater[201] (see also [202, 203, 204, 205, 206, 207]). Ethyl 2-furoate, in ether or toluene, was refluxed for several hours with the Grignard reagent, reaction proceeding normally to give on subsequent hydrolysis, the appropriate tertiary alcohol (II) in high yield. Similar results were obtained using 2,5-furandicarboxylic ester.[201] It is interesting to note, however, that when

$$C_4H_3O\text{—}COOR + 2R'MgX \rightarrow C_4H_3O\text{—}C(OH)R'_2$$
$$\text{II}$$

the reaction is applied to 5-halo-2-furoic esters, it has not been possible to isolate the expected 5-halo-2-furylcarbinols (footnote [g], p. 646).

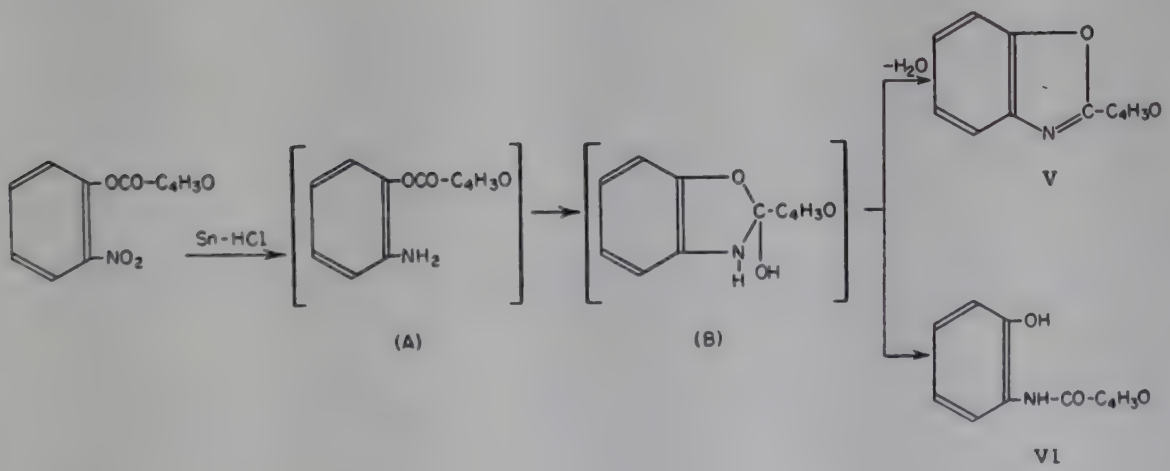
In the recent work of Kuznetsov,[208] furoic acid was treated with an excess of the Grignard reagent in boiling xylene. Under these conditions, there was obtained, not only the expected ketone and tertiary alcohol, but

[194] Musante and Berretti, *Gazz. chim. ital.*, **79**, 683 (1949); *C. A.*, **44**, 4457 (1950).
[195] Semmler and Ascher, *Ber.*, **42**, 2355 (1909).
[196] Sprague, Beckham and Adkins, *J. Am. Chem. Soc.*, **56**, 2665 (1934).
[197] Shalygin, *J. Gen. Chem. U.S.S.R.*, **15**, 375 (1945); *C. A.*, **40**, 3752 (1946).
[198] Harris and Levine, *J. Am. Chem. Soc.*, **71**, 1120 (1949).
[199] McElvain and Weber, *J. Am. Chem. Soc.*, **63**, 2192 (1941).
[200] Calingaert, Soroos, Hnizda and Shapiro, *J. Am. Chem. Soc.*, **62**, 1545 (1940).
[201] Hale, McNally and Pater, *Am. Chem. J.*, **35**, 68 (1906).
[202] Mahood and Aldrich, *J. Am. Chem. Soc.*, **52**, 4477 (1930).
[203] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15**, 1118 (1932).
[204] Ushakov and Kucherov, *J. Gen. Chem. U.S.S.R.*, **14**, 1073 (1944); *C. A.*, **40**, 7185 (1946).
[205] French and Smith, *J. Am. Chem. Soc.*, **67**, 1949 (1945).
[206] Bachman and Heisey, *J. Am. Chem. Soc.*, **71**, 1985 (1949).
[207] Dounce, Wardlow and Connor, *J. Am. Chem. Soc.*, **57**, 2556 (1935).
[208] Kuznetsov, *J. Gen. Chem. U.S.S.R.*, **12**, 631 (1942); *C. A.*, **38**, 1494 (1944).

in addition, the appropriate furyltrialkylmethane (III) by reduction, and also an unsaturated diketone, IV, as a result of cleavage of the nucleus.

$$C_4H_3O\text{—}COOH \xrightarrow{RMgX} \begin{array}{c} C_4H_3O\text{—}COR \\ + \\ C_4H_3O\text{—}C(OH)R_2 \\ + \\ C_4H_3O\text{—}CR_3\ (III) \\ + \\ RCH{=}CHCH_2COCOR\ (IV) \end{array}$$

Reduction of *o*-nitrophenyl 2-furoate with tin and hydrochloric acid at 0° gives 2-(2-furyl)benzoxazole, V. At more elevated temperatures, only a small amount of V may be isolated, the major product being N-(*o*-hydroxyphenyl)-2-furamide [*o*-2-furamidophenol], VI. This behavior is similar to that exhibited by *o*-nitrophenyl benzoate, and the reaction may proceed via intermediates A and B, neither of which was isolated.[172] Similar reduction of related *o*-nitrophenyl 2-furoates possessing a bromine atom in the benzene nucleus yielded the corresponding bromine substituted derivatives of V and VI, the latter predominating. When two bromine atoms were so situated, reduction led exclusively to the appropriate furamidophenol.[172] It has not been observed whether VI, like *o*-benzamidophenol,[209] will cyclize on heating above the melting point to give the appropriately substituted benzoxazole.



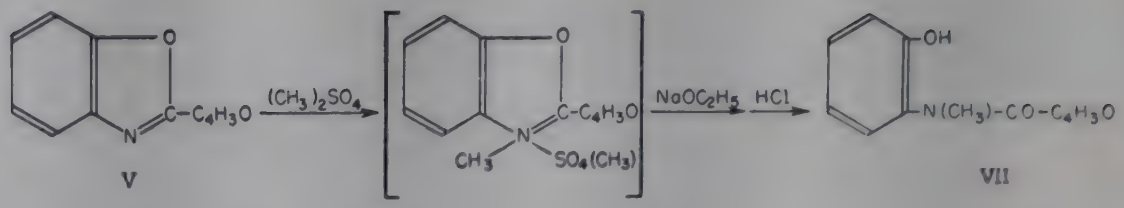
Furylbenzoxazoles

In addition to the method of preparation illustrated above, 2-(2-furyl)benzoxazole has been prepared by heating an equimolecular mixture of 2-furoic acid and *o*-aminophenol at 150–200° until the theoretical amount of water is liberated.[210] Treatment with methyl sulfate gives a quaternary salt of the base which is transformed, by the action of sodium ethoxide, into N-methyl-N-*o*-hydroxyphenyl-2-furamide, VII.[210]

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[209] Hübner, *Ann.*, **210**, 328 (1881).

[210] I. G. Farbenind., French Patent 744,491 (1934); *C. A.*, **29**, 2178 (1935).

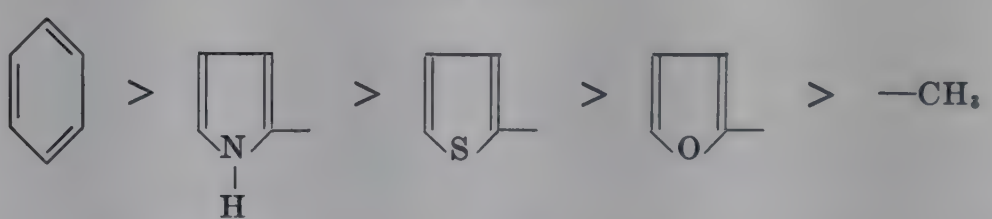


V VII

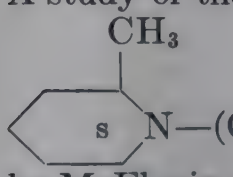
Compound V and related types

Substituents in benzene nucleus	Crystal form	M.p. (°C.)	Ref.
Unsubstituted	colorless plates	86, 83–85	210, 172
5-Bromo-	pale brown prisms	92–93	172
5-Bromo-6-methyl-	colorless needles	122–124	172

A variety of N-substituted aminoalkyl esters[h] of 2-furoic acid have been prepared, and evaluated from the standpoint of their physiological action. Mudzhoyan[212] (see also [213]) reports these esters to be local anesthetics comparable to novocaine and less toxic. The corresponding esters of 5-bromo-2-furoic acid were also tested and found to be yet more potent in their anesthetic action, but also more toxic.[214] With 1-(dimethylaminomethyl)-1-methylpropyl 2-furoate, Buchel and Meyer[215] observed that it was only about one-half as potent as a local anesthetic as the corresponding benzoic ester (stovaine). Within the group of compounds studied by them, Gilman and Pickens[168] had earlier noted the 2-furyl radical to be less active in its effect upon local anesthesia than the phenyl group and, at that time, rated several radicals in the order shown below:



A study of the relative influence of these groups when present as the R in



(metycaine where R = C_6H_5) is reported by McElvain and Carney.[216] The related 1-piperidino-2,3-propanediol di-2-

[h] The action of various sera containing azolesterases (enzymes which hydrolyze esters of nitrogen-containing alcohols) on furoic esters of this type was studied by Glick.[211]

[211] Glick, *J. Am. Chem. Soc.*, **64**, 564 (1942).
[212] Mudzhoyan, *J. Gen. Chem. U.S.S.R.*, **16**, 751 (1946); *C. A.*, **41**, 2033 (1947).
[213] Cook and Kreke, *J. Am. Chem. Soc.*, **62**, 1951 (1940).
[214] Mudzhoyan, *J. Gen. Chem. U.S.S.R.*, **16**, 767 (1946); *C. A.*, **41**, 2033 (1947).
[215] Buchel and Meyer, *Compt. rend. soc. biol.*, **141**, 32 (1947); *C. A.*, **41**, 5971 (1947)
[216] McElvain and Carney, *J. Am. Chem. Soc.*, **68**, 2592 (1946).

TABLE 5. N-SUBSTITUTED AMINOALKYL ESTERS OF 2-FUROIC ACID

Aminoalkyl group	Physical constants and derivatives (°C.)	Ref.
2-(Dimethylamino)ethyl	b.p. 145–146 (20 mm.) hydrochloride, m.p. 183 picrate, m.p. 155–156	212
2-(Diethylamino)ethyl	b.p. 135 (22 mm.) hydrochloride, m.p. 131–132 picrate, m.p. 105–106	168, 213, 212
2-(Dibutylamino)ethyl	hydrobromide, m.p. 91–92	213
2-(Ethylphenylamino)ethyl	hydrobromide, m.p. 119.5–122.5	213
3-(Dimethylamino)propyl	b.p. 134–135 (20 mm.) hydrochloride, m.p. 157 picrate, m.p. 189–190	212
3-(Diethylamino)propyl	b.p. 173 (15 mm.) hydrochloride, m.p. 132–134 picrate, m.p. 110–112	212, 213
3-(Dipropylamino)propyl	b.p. 167–168 (11 mm.) hydrochloride, m.p. 113	212
3-(Dibutylamino)propyl	hydrobromide, m.p. 93.6–95.6	213
3-(2-Methylpiperidino)propyl	hydrochloride, m.p. 126–128	216
2,2′-Bis(dimethylamino)-*i*-propyl	b.p. 158–159 (19 mm.) hydrochloride, m.p. 126 picrate, m.p. 220–221	212
2,2′-Bis(diethylamino)-*i*-propyl	b.p. 191–192 (12 mm.) hydrochloride, m.p. 139 picrate, m.p. 155–156	212
2,2′-Bis(dipropylamino)-*i*-propyl	b.p. 180–182 (16 mm.) picrate, m.p. 141–142	212
2,2′-Bis(diallylamino)-*i*-propyl	b.p. 186–187 (17 mm.) picrate, m.p. 140–141	212
2,2′-Bis(dibutylamino)-*i*-propyl	b.p. 186–187 (16 mm.) picrate, m.p. 130–131	212
2,2′-Bis(di-*i*-butylamino)-*i*-propyl	b.p. 182–185 (17 mm.) picrate, m.p. 128–129	212

TABLE 5.—*Continued*

Aminoalkyl group	Physical constants and derivatives (°C.)	Ref.
1-(Dimethylaminomethyl)-1-methylpropyl	b.p. 125–126 (14 mm.) hydrochloride, m.p. 193.5 picrate, m.p. 120–121	212
1-(Diethylaminomethyl)butyl	b.p. 142–143 (4 mm.)	212
3-(Dimethylamino)-1,2-dimethylpropyl	b.p. 136–137 (19 mm.) hydrochloride, m.p. 147	212
3-(Diethylamino)-1,2-dimethylpropyl	b.p. 165–166 (22 mm.) hydrochloride, m.p. 163 picrate, m.p. 142–143	212
1-(Dipropylamino)-1,2-dimethylpropyl	b.p. 180–181 (17 mm.) picrate, m.p. 155–156	212
3-(Dimethylamino)-2,2-dimethylpropyl	b.p. 125–126 (16 mm.) hydrochloride, m.p. 155 picrate, m.p. 126–127	212
3-(Diethylamino)-2,2-dimethylpropyl	b.p. 163 (22 mm.) hydrochloride, m.p. 170 picrate, m.p. 115–116	212
3-(Dipropylamino)-2,2-dimethylpropyl	b.p. 167–168 (21 mm.) picrate, m.p. 106–107	212
3-(Di-*i*-butylamino)-2,2-dimethylpropyl	b.p. 175–176 (19 mm.) picrate, m.p. 89–90	212

furoate, m.p. 73–74°, was investigated by Walter[217] as was the corresponding diester obtained from 3-(2-furyl)acrylyl chloride and piperidinopropanediol.

Phatak and Emerson[218] observed that the toxicity of the lower alkyl 2-furoates, on intraperitoneal injection in rats, increases from methyl to propyl; that the lesser toxicity of the butyl and pentyl esters was probably attributable to their lesser solubility. They further noted that the local anesthetic activity of these esters increases from methyl to pentyl, a property considered to be of purely academic interest in view of the results reported earlier by Gilman and Pickens.[168] For the enzymatic hydrolysis of the aminoalkyl esters, see Glick.[211]

[217] Walter, *J. Am. Chem. Soc.*, **60**, 2467 (1938).
[218] Phatak and Emerson, *J. Pharmacol. Exptl. Therap.*, **58**, 174 (1936).

The esters derived from 2-furoyl chloride and *o*-hydroxycarboxylic acids of the benzene series (particularly furoylsalicylic acid) are reported to have excellent analgesic and antipyretic properties.[175, 173, 174]

2-Furoyl Halides. Of the 2-furoyl halides, both the chloride and bromide have been described. The former was first prepared by Liès-Bodard[219] by the action of phosphorus pentachloride on the free acid. Others[85, 3, 220] employed the same reagent, the reported yield of acid chloride varying in the range from 70–80 per cent[221] to almost the theoretical quantity.[25]

Phosphorus trichloride may also be employed. Reichstein and Morsman[222] obtained 2-furoyl chloride in 77 per cent yield by interaction of this reagent and furoic acid, although Hill and Sawyer[223] had previously reported failure by this method.

A patented procedure[224] involves treatment of 2-furoic acid with phosgene at superatmospheric pressure.

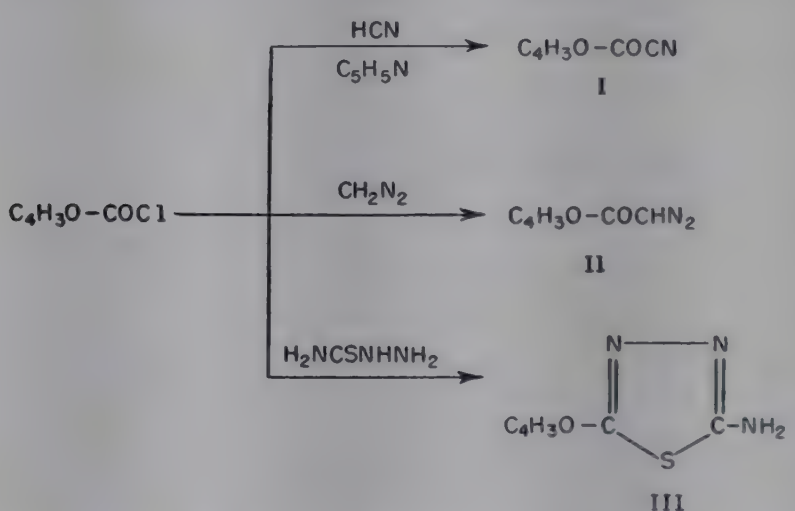
The most widely employed synthesis of 2-furoyl chloride, however, has been that in which furoic acid is mixed with thionyl chloride. The yields reported by the many investigators vary rather widely. Thus, Baum,[170] Gelissen and Van Roon,[225] and more recently, Mudzhoyan[212] claim almost quantitative conversion to the acid chloride. On the other hand, Bogert and Stull[226] and Douglass and Dains[227] report yields in the neighborhood of 70–80 per cent, and Maxim[221] obtained only 40 per cent. Gilman and Hewlett[228] conducted the reaction in dry benzene, thereby obtaining 2-furoyl chloride in 75 per cent yield. By a modification of this procedure, Hartmann and Dickey[229] were able to produce the chloride on a larger scale (2.5–3 kilogram batches) in 90 per cent yield. These workers attributed the variable yields reported in the literature to impurities in the reactants, and later, Holdren and Barry[164] observed that such impurities may act to catalyze hydrolysis and thus impair the yield unless adequate precautions are taken to completely exclude moisture from the reaction mixture.

[219] Liès-Bodard, *Ann.*, **100**, 325 (1856); *Compt. rend.*, **43**, 391 (1856).
[220] Chavanne, *Compt. rend.*, **134**, 1439 (1902).
[221] Maxim, *Bul. soc. chim. Romania*, **12**, 33 (1930); *Chem. Centr.*, **1930, II**, 3023.
[222] Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).
[223] Hill and Sawyer, *Am. Chem. J.*, **20**, 169 (1898).
[224] Meuser (to Dominion Rubber Co., Ltd.), Canadian Patent 373,516 (1938); *C. A.*, **32**, 5003 (1938).
[225] Gelissen and Van Roon, *Rec. trav. chim.*, **43**, 359 (1924).
[226] Bogert and Stull, *J. Am. Chem. Soc.*, **48**, 248 (1926).
[227] Douglass and Dains, *J. Am. Chem. Soc.*, **56**, 719 (1934).
[228] Gilman and Hewlett, *Iowa State Coll. J. Sci.*, **4**, 27 (1929).
[229] Hartmann and Dickey, *Ind. Eng. Chem.*, **24**, 151 (1932).
[230] Burger and Harnest, *J. Am. Chem. Soc.*, **65**, 2382 (1943).
[231] Kodak Ltd., Knott, Hamer and Rathbone, British Patent 594,558 (1947); *C. A.*, **42**, 4079 (1948).
[231a] Collonna and Parravano, *Ann. chim. applicata*, **38**, 434 (1948); *C. A.*, **44**, 128 (1950).
[232] Baum, *Ber.*, **34**, 2505 (1901).

Direct synthesis of 2-furoyl chloride from furfural by the action of chlorine has not been successful. Schneider[26] investigated this procedure, but failed to find suitable experimental conditions; nuclear chlorination could not be avoided.

2-Furoyl bromide: $C_4H_3O—COBr$; b.p. 78° (11 mm.); in 77 per cent yield by refluxing furoic acid with phosphorus tribromide for one hour.[222]

2-Furoyl chloride is a colorless liquid which boils at 173° at atmospheric pressure; b.p. 58° (12 mm.). It exerts a powerful lachrymatory action and is, therefore, highly disagreeable to work with unless adequate ventilation is provided. In the pure state it resists hydrolysis, and is only very slowly decomposed by boiling water.[164] Like other acyl halides, 2-furoyl chloride reacts readily with alcohols to form esters, and with ammonia and amines to give the corresponding 2-furamides. With anhydrous hydrogen cyanide and pyridine, the nitrile, I, of furoylformic acid is obtained,[222] and the action of diazomethane produces the diazo ketone, II.[230, 231] Inasmuch as these reactions are considered elsewhere, under the type of product obtained, no further comment is needed here. With thiosemicarbazide in the



Freundl-Meinecke synthesis, furoyl chloride gives rise to 2-amino-5-(2-furyl)-1,3,4-thiadiazole, III (2-*p*-aminophenylsulfonamido derivative, m.p. 258–259°).[231a]

2-Furoic Anhydrides. 2-Furoic anhydride, $(C_4H_3O—CO)_2O$, is a crystalline product melting at 71–73° and boiling at 196–197° (22 mm.), (b.p. 350° with decomposition at atmospheric pressure). It is soluble in alcohol and ether, and is quite stable to water and cold aqueous alkali[232] (see also [233, 234]).

Baum[232] obtained the anhydride by heating 2-furoyl chloride with sodium or silver furoate. Later, Katsnel'son and Gol'dfarb[180] (see also [235]) prepared

[233] Smith and Bryant, *J. Am. Chem. Soc.*, **58**, 2452 (1936).
[234] Smith, Bryant and Mitchell, *J. Am. Chem. Soc.*, **63**, 1700 (1941).
[235] Katznel'son and Gol'dfarb, Russian Patent 39,762 (1934); *C. A.*, **30**, 3443 (1936)

it in 75 per cent yield by refluxing the acid chloride with acetic anhydride in toluene. Yet more recently, Adkins and Thompson[236] have reported its synthesis by the action of water on the solid addition compound from furoyl chloride and pyridine.

Hurd and Dull[237] obtained 2-furoic acetic anhydride, I, in quantitative yield by passing ketene into a solution of furoic acid in ether. The mixed anhydride is an oil which when subjected to distillation, undergoes disproportionation to the symmetrical anhydrides. With aniline, it gives furoic acid and acetanilide exclusively; no furanilide was formed.

$$C_4H_3O{-}COOH \xrightarrow{CH_2{=}C{=}O} C_4H_3O{-}CO{-}O{-}COCH_3$$

I

heat → $(C_4H_3O{-}CO)_2O + Ac_2O$

$C_6H_5NH_2$ → $C_4H_3O{-}COOH + C_6H_5NHCOCH_3$

Furoyl Peroxide and Furoyl Hydrogen Peroxide. 2-Furoyl peroxide, I, has been obtained in excellent yield by conventional procedures. It was first described by Gelissen and Van Roon.[225] Their synthesis placed hydrogen peroxide in reaction with 2-furoyl chloride in the presence of alkali. Later, Milas and McAlevy[238] isolated it in 96 per cent yield from the acid chloride and sodium peroxide.

$$C_4H_3O{-}COCl \xrightarrow{Na_2O_2} C_4H_3O{-}CO{-}O{-}O{-}CO{-}C_4H_3O$$

I

2-Furoyl peroxide is a white, or pale yellow, crystalline compound, m.p. 86–87° (dec.); soluble in ether, alcohol, acetone, chloroform and benzene. It deflagrates on heating or rubbing, and is more sensitive toward percussion than benzoyl peroxide. Unlike the latter, it precipitates iodine from aqueous potassium iodide, no doubt as a consequence of the greater ease of hydrolysis of the furan analog. As a catalyst for the solution-polymerization of *l*-menthyl acrylate, furoyl peroxide exhibited a great deal less activity than several substituted benzoyl peroxides with which it was compared.[239]

Reaction of furoyl peroxide with sodium methoxide in methyl alcohol proceeds in normal fashion, and on working up the mixture, furoyl hydrogen peroxide (perfuroic acid) is obtained.[238] To date, the pure peracid has been isolated in no other manner.[i]

[i] Whereas benzoyl hydrogen peroxide is formed in good yield by the autoxidation of benzaldehyde, attempts to produce furoyl hydrogen peroxide from furfural in this manner have resulted in failure. Milas and McAlevy[238] did succeed in isolating a small

$$C_4H_3O{-}CO{-}O{-}O{-}CO{-}C_4H_3O \xrightarrow{NaOCH_3} \xrightarrow{H^+} C_4H_3O{-}\overset{\overset{O}{\|}}{C}{-}O{-}OH$$

Furoyl hydrogen peroxide, m.p. 59.5° (dec.), is soluble in the common solvents with the exception of petroleum ether. The solid peracid decomposes spontaneously at 35°, yielding furoic acid, carbon dioxide and polymer. Decomposition at room temperature is brought about by contact with certain types of inorganic and organic solids, and by exposure to ultraviolet light. In chloroform solution the decomposition, predominantly to furoic acid and oxygen, proceeds in accordance with the unimolecular law, the rate being expressed by the equation, $k = 1.035 \times 10^9 e^{-15,800/RT}$.[240]

At 0°, particularly in chloroform solution, furoyl hydrogen peroxide is reasonably stable, and may be used for the quantitative estimation of double bonds in several organic substances.[238]

Thio- and Dithiofuroic Acids. Thiofuroic acid, m.p. −9°, b.p. 101–103° (16 mm.), n_D^{24} 1.589, is a yellow oil which is obtained by the action of sodium hydrogen sulfide on furoyl chloride.[241] It is insoluble in water and is miscible with alcohol and ether. Thiofuramide, m.p. 127°.[242] Derivatives of thiofuroic acid prepared from furoyl chloride and substituted mercaptobenzothiazoles are reported to be useful as vulcanization accelerators.[243]

Like other thioacids, thiofuroic acid is easily oxidized, and on standing in contact with air is converted into furoyl disulfide, a white crystalline solid, m.p. 107–108°,[241] which has also been prepared by treatment of furoyl chloride with alcoholic sodium disulfide.[239] When evaluated as a promoter of the emulsion copolymerization of butadiene and styrene, furoyl disulfide exhibited no activity, differing in this respect from the aroyl disulfides.[239]

$$C_4H_3O{-}COCl \xrightarrow{NaSH} C_4H_3O{-}CO{-}SH \xrightarrow{(O)} (C_4H_3O{-}CO)_2S_2$$

$$\xrightarrow{Na_2S_2} \uparrow$$

quantity of white solid which reacted with potassium iodide as though it contained some peracid. However, they were unable to separate the latter in the pure state, hence it was not possible to identify it with authentic perfuroic acid. It appears that only a minor proportion of furfural is autoxidized to the peracid; that the major reaction proceeds by an entirely different mechanism (see p. 385).

[236] Adkins and Thompson, *J. Am. Chem. Soc.*, **71**, 2242 (1949).

[237] Hurd and Dull, *J. Am. Chem. Soc.*, **54**, 3427 (1932).

[238] Milas and McAlevy, *J. Am. Chem. Soc.*, **56**, 1219 (1934).

[239] Frank, Blegen and Deutschman, *J. Polymer Sci.*, **3**, 58 (1948).

[240] Milas and McAlevy, *J. Am. Chem. Soc.*, **56**, 1221 (1934).

[241] Patton, *J. Am. Chem. Soc.*, **71**, 3571 (1949).

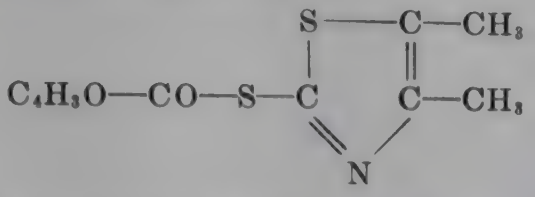
[242] Douglass, *Ber.*, **25**, 1311 (1892).

[243] Evans, (to The Rubber Service Laboratories), U. S. Patent 2,020,051 (1935); *C. A.*, **30**, 650 (1936).

Thiofuroic, 2-thenylmethyl ester: $C_4H_3O—CO—SCH_2—C_4H_3S$; m.p. 55°; by reaction of furoyl chloride with 2-thenylmethyl mercaptan in excess pyridine.[244]

3-Thienyl thiofuroate: $C_4H_3O—CO—S—C_4H_3S$; m.p. 51–52°; from furoyl chloride and 3-thiophenethiol.[244a]

4,5-Dimethyl-2-(2-furoyl)mercaptothiazole:



m.p. 90–91°; from furoyl chloride and 4,5-dimethyl-2-mercaptothiazole.[244b]

A patented process for the production of dithiofuroic acid, $C_4H_3O—CSSH$, involves the addition of furfural and sulfuric acid to aqueous sodium sulfide and sulfur[245] (see also [246]). However, the use of ammonium polysulfide is reported to give better results,[247] the free dithioacid being liberated as a red, oily liquid following acidification of the ammonium salt. The cyclohexylammonium salt (m.p. 113–114°, dec.) and other amine salts are formed directly by treatment of furfural with hydrogen sulfide, sulfur and the appropriate amine.[248, 249] The phthalimidomethyl ester of dithiofuroic acid melts at 149–153°.[250]

Oxidation of dithiofuroic acid by the oxygen of the air, or by means of potassium ferricyanide produces dithiofuroyl disulfide, $(C_4H_3O\text{-}CS)_2S_2$ (m.p. 93°, 100–101°), reddish-purple crystals from acetone.[247, 251, 246] For the chloromethylation of ammonium dithiofuroate, see Hardman.[252]

2-Furamide and Related Compounds. 2-Furamide and its N-substituted derivatives[j] are obtained in the usual manner by the action of ammonia, or primary or secondary amines on 2-furoic ester. They are also formed smoothly using the acid chloride in place of the ester, except in one reported instance; condensation with methylamine failed to give the expected furo-

[j] The known 2-furimido-alkyl esters, tautomers of the 2-furoalkylamides, are mentioned under 2-furonitrile (p. 546) from which they are derived.

[244] Kipnis, Levy and Ornfelt, *J. Am. Chem. Soc.*, **71**, 3570 (1949).

[244a] Brooks, Howard and Wehrle, *J. Am. Chem. Soc.*, **72**, 1289 (1950).

[244b] Stewart and Mathes, *J. Org. Chem.*, **14**, 1111 (1949).

[245] Leuck, (to The Quaker Oats Co.), U. S. Patent 1,756,158 (1930); *C. A.*, **24**, 3022 (1920).

[246] Alliger, Smith, Carr and Stevens, *J. Org. Chem.*, **14**, 962 (1949).

[247] Bruni, *Giorn. chim. ind. applicata*, **4**, 533 (1922); *C. A.*, **17**, 1635 (1923).

[248] Hardman, (to Wingfoot Corp.), U. S. Patent 2,386,111 (1945); *C. A.*, **40**, 764 (1946).

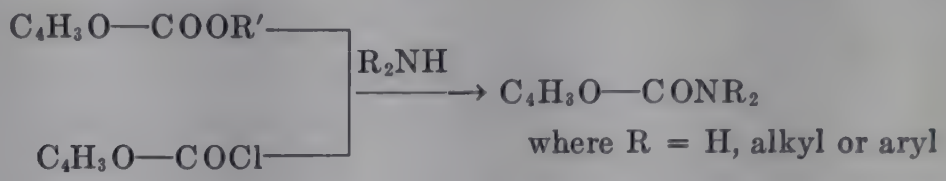
[249] Hardman, (to Wingfoot Corp.), U. S. Patent 2,469,824 (1949); *C. A.*, **43**, 6666 (1949).

[250] Watt, (to Wingfoot Corp.), U. S. Patent 2,256,157 (1941); *C. A.*, **36**, 295 (1942).

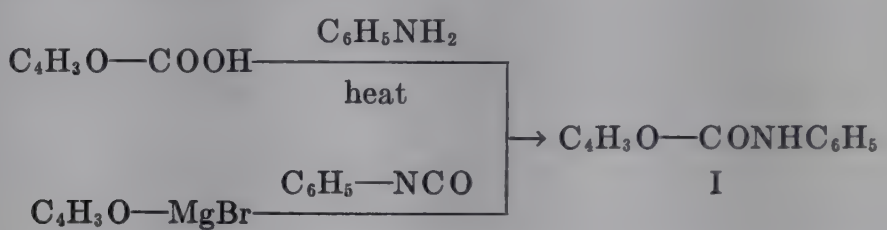
[251] Bruni and Levi, *Atti accad. Lincei*, **32**, I, 5 (1923); *C. A.*, **18**, 2693 (1924); *Gazz. chim. ital.*, **54**, 389 (1924).

[252] Hardman, (to Wingfoot Corp.), U. S. Patents 2,515,119 and 2,522,268 (1950).

methylamide.[170] By saturating an ether solution of 2-furoyl chloride with ammonia, 2-furamide is formed in 95 per cent yield[228] (see also [253, 254]).



The amides are also obtained by heating the appropriate ammonium salts ($C_4H_3O—COONH_3R$, where R = H, alkyl or aryl).[255, 69] In this connection it is reported that the velocity of reaction on heating 2-furoic acid with aniline is greater than with ammonia, and the yield of 2-furanilide, I, so obtained is more than that of the unsubstituted amide formed in the latter instance.[256] 2-Furanilide has also been synthesized from 2-furylmagnesium bromide and phenyl isocyanate.[257]



Attempted synthesis of 2-furamide by the action of ammonium persulfate on furfural has not been successful.[258] However, furfural oxime is readily rearranged to 2-furamide when heated in contact with Raney nickel, a procedure which Paul[259, 260] has recommended as suitable for the commercial production of the latter. Earlier, Yamaguchi[261] reported formation of the amide by passing furfural oxime over reduced copper at 200° in an atmosphere of hydrogen. Similarly, 2-furyl phenyl ketoxime undergoes the Beckmann rearrangement to give 2-furanilide[153] (see also [262]), but the yield is very poor.

$$C_4H_3O—CH{=}NOH \rightarrow C_4H_3O—CONH_2$$

The 2-furamides are, in general, more soluble than the corresponding benzamides. On hydrolysis, they give 2-furoic acid and the appropriate

[253] Ciamician and Dennstedt, *Ber.*, **14**, 1058 (1881).
[254] Wallach, *Ann.*, **214**, 193 (1882).
[255] Schiff, *Ann.*, **239**, 349 (1887).
[256] Amitin and Litkevich, *Trav. inst. chim. Charkov*, **1**, 33 (1935); *C. A.*, **32**, 4149 (1938).
[257] Shepard, Winslow and Johnson, *J. Am. Chem. Soc.*, **52**, 2083 (1930).
[258] Pickard and Carter, *J. Chem. Soc.*, **79**, 520 (1901).
[259] Paul, *Bull. soc. chim.* (*5*), **4**, 1115 (1937).
[260] Paul, *Compt. rend.*, **204**, 363 (1937).
[261] Yamaguchi, *Bull. Chem. Soc. Japan*, **1**, 35 (1926); *C. A.*, **21**, 75 (1927).
[262] Vargha and Gönczy, *J. Am. Chem. Soc.*, **72**, 2738 (1950).

TABLE 6. SOME 2-FURAMIDES

Compound	M.p. (°C.)	Ref.
2-Furamide	142	219, 28, 253, 254, 11, 263, 228, 259
N-Substituted 2-furamides		
Substituent:		
methyl	60, 64	264, 158
	b.p. 144–145 (18 mm.)	
ethyl	b.p. 258 (—)	254
propyl	39–40	265
n-butyl	40–41	265
i-butyl	122–123	265
tert.-butyl	99	265
n-pentyl	31–32	265
i-pentyl	48–56	265
2-methylbutyl	53–54	265
3,3-dimethylpropyl	68–69	265
hexyl (1-methyl-*i*-pentyl)	54–55	265
octyl (2-ethylhexyl)	oil	265
dodecyl	57–58	69
octadecyl	79.5–80.5	69
cyclohexyl	112–112.5, 108.5–109	266, 265
benzyl	111	266, 267
phenyl	121–122, 123.5	257, 170; see also 255, 262
o-tolyl	62	170
m-tolyl	87	170
p-tolyl	107.5	170
2,3-xylyl	118	268
2,4-xylyl	96, 104–105	268, 170
2,5-xylyl	89–90	268, 170
2,6-xylyl	101, 125–126	268, 170
3,4-xylyl	97	268
o-hydroxyphenyl	161–162	172
p-methoxyphenyl	105–106	262
m-chlorophenyl	116	268
p-chlorophenyl	146	268
m-nitrophenyl	147–148	269
m-aminophenyl	142–143	269
p-acetamidophenyl	215	268
3-amino-4-methylphenyl	116–117	269
2-methyl-4-nitrophenyl	166	269
3-nitro-4-methylphenyl	126	269
2-methoxy-4-aminophenyl	124	269
2-methoxy-5-aminophenyl	133–134	269

TABLE 6.—*Continued*

Compound	M.p. (°C.)	Ref.
2-methoxy-4-nitrophenyl	181–182	269
2-methoxy-5-nitrophenyl	165	269
2-chloro-5-aminophenyl	169–171	269
2-chloro-5-nitrophenyl	180–183	269
2-hydroxy-5-bromophenyl	238	269
2-methyl-4-amino-5-methoxyphenyl	134	270
2-methoxy-4-amino-5-methylphenyl	169	270
2-methyl-4-nitro-5-methoxyphenyl	175	270
2-methoxy-4-nitro-5-methylphenyl	170	270
2,5-dimethoxy-4-nitrophenyl	174	269
2-methoxy-4-amino-5-chlorophenyl	181.5	270
2-methoxy-4-nitro-5-chlorophenyl	194.5	270
2-hydroxy-4-methyl-5-bromophenyl	239–240	172
2,4,6-tribromophenyl	164	271
o-biphenyl	76, 76–77.5 b.p. 260 (24 mm.)	268, 272
p-biphenyl	168 (dec.), 171–172	268, 266
1-naphthyl	151–152, 155–156	268, 266
2-naphthyl	152–153	268, 266
2-fluorenyl	201–201.5	266
xanthyl	209–211	273
Miscellaneous		
N,N-diethyl-2-furamide	23 b.p. 140 (20 mm.)	221
N-methyl-2-furanilide	125, 120	271, 274
N-ethyl-2-furanilide	127	274
N-phenyl-2-furanilide	157	274
N-methyl-*o*-hydroxy-2-furanilide	221–222	210
2-furopiperidide	57, 58 b.p. 160–165 (20 mm.)	170, 275
N,N′-ethylenebis-2-furamide	200	268
N,N′-di-2-furoyl-2,4-toluenediamine	193	268
N,N′-di-2-furoylbenzidine	>310	268
N,N′-di-2-furoylbis(4-aminophenyl)-sulfone	286	226
o-2-furamidophenyl disulfide	160.5	172
N-2-furoylbenzoxazolone	141–143	276

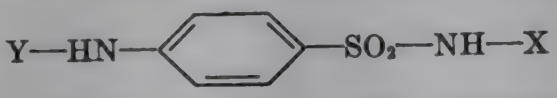
[263] Freundler, *Bull. soc. chim.* (*3*), **17**, 419 (1897).
[264] Wheeler and Atwater, *Am. Chem. J.*, **23**, 145 (1900).
[265] Degnan and Pope, *J. Am. Chem. Soc.*, **62**, 1960 (1940).
[266] Bowen and Smith, *J. Am. Chem. Soc.*, **62**, 3522 (1940).
[267] Dermer and King, *J. Org. Chem.*, **8**, 168 (1943).
[268] Buu-Hoi and Nguyan-Hoan, *Rec. trav. chim.*, **68**, 5 (1949).
[269] Etzelmiller (to E. I. du Pont de Nemours & Co.), U. S. Patent 2,144,220 (1939); *C. A.*, **33**, 3172 (1939).

amino compound, fission of the C-N link occurring more easily in alkaline medium than is the case with the benzene analogs.[170]

TABLE 7. COMPARATIVE SOLUBILITY OF SOME 2-FURAMIDO AND BENZAMIDO COMPOUNDS[170]

Compound	Solvent	Temp. (°C.)	Solubility pts./100 pts. solvent
2-Furanilide	abs. EtOH	30	11.5
Benzanilide	abs. EtOH	30	4.1
2-Furo-*p*-toluidide	abs. EtOH	18.5	11.2
Benzo-*p*-toluidide	abs. EtOH	18.5	4.2
N-*m*-tolyl-2-furamide	abs. EtOH	15	33.4
N-*m*-tolyl-2-benzamide	abs. EtOH	15	12.7
N,N′-ethylenebis-2-furamide	abs. EtOH	15.5	0.42
N,N′-ethylenebisbenzamide	abs. EtOH	15.5	0.07
N-2-furoylglycine	H_2O	20.5	3.2
N-benzoylglycine (hippuric acid)	H_2O	20.5	0.4
N-2-furoylalanine	H_2O	14	0.8
N-benzoylalanine	H_2O	cold	0.4
α-2-Furamidophenylacetic acid	H_2O	17	0.14
α-2-Benzamidophenylacetic acid	H_2O	17	0.14
2-Furophenylhydrazide	abs. EtOH	17	3.6
2-Benzophenylhydrazide	abs. EtOH	25	2.4

TABLE 8. N-2-FUROYLSULFANILAMIDES

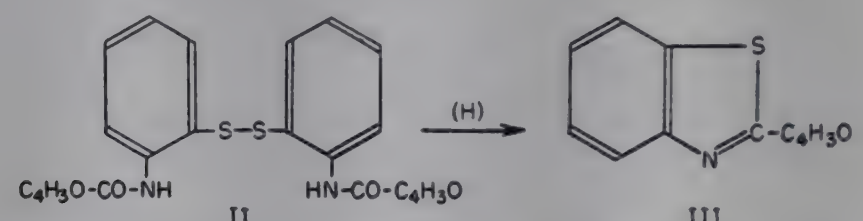


Compound		M.p. (°C.)	Ref.
Y	X		
Hydrogen	2-furoyl	191.5–192	277, 278, 279, 280, 281
Hydrogen	5-*t*-butyl-2-furoyl	239	282, 283, 284
Acetyl	2-furoyl	240.5–241.5	277
Carbethoxy	2-furoyl	259 (dec.)	278
2-Furoyl	hydrogen	273.5	285, 286
2-Furoyl	2-furoyl	255 (dec.)	287
2-Furoyl	phenyl	243.5–244	285
2-Furoyl	*p*-nitrophenyl	259	285
2-Furoyl	*p*-aminophenyl	238–238.5	285
2-Furoyl	2-pyridyl	242	285

In reactions involving the amido group, the 2-furamides behave more or less normally, although some complexities appear when the attacking reagent affects the furan nucleus.

Catalytic hydrogenation of 2-furamide over copper-chromium oxide gives a mixture of primary and secondary 2-furfurylamines. In this reaction, as with other amides, it is desirable to employ dioxane as a solvent to minimize hydrolysis due to the water formed on reduction.[288, 289]

On reduction, using tin and hydrochloric acid, *o*-2-furamidophenyl disulfide, II, cyclizes with the formation of 2-(2-furyl)benzothiazole, III[k] (m.p. 105°), which is also obtainable by the direct action of 2-furoyl chloride on zinc *o*-aminophenyl mercaptide[226] and by condensation of furfural with *o*-aminophenyl mercaptan.[291]



II III

2-Furamide is converted into the nitrile, by the action of phosphorus

[k] 2-(2-Furyl)benzoselenothiazole, m.p. 133°, is also known. Preparation involved reaction of furoyl chloride with zinc *o*-aminoselenophenolate.[290]

[270] Kizhner and Krasova, *Anilinokrasochnaya Prom.*, **3**, 430 (1933); *C. A.*, **28**, 3729 (1934).

[271] Gilman and Young, *J. Am. Chem. Soc.*, **56**, 464 (1934).

[272] Mamalis and Petrow, *J. Chem. Soc.*, **1950**, 703.

[273] Phillips and Pitt, *J. Am. Chem. Soc.*, **65**, 1355 (1943).

[274] Maxim, Zugravescu and Fulga, *Bull. soc. chim.*, **6**, 1339 (1939).

[275] Asano and Nakatomi, *J. Pharm. Soc. Japan*, **53**, 176 (1933); *C. A.*, **27**, 2703 (1933).

[276] Zasosov, *J. Gen. Chem. U.S.S.R.*, **17**, 471 (1947); *C. A.*, **42**, 534 (1948).

[277] Crossley, Northey and Hultquist, *J. Am. Chem. Soc.*, **61**, 2950 (1939).

[278] Dohrn and Diedrich, (to Schering Corp.), U. S. Patent 2,411,495 (1946); *C. A.*, **41**, 4809 (1947).

[279] Martin and Häfliger, (to Geigy A.-G.), U. S. Patent 2,417,005 (1947); *C. A.*, **41**, 5898 (1947).

[280] Martin, Häfliger and Neracher, (to Geigy A.-G.), U. S. Patent 2,417,006 (1947); *C. A.*, **41**, 5898 (1947).

[281] Geigy, A.-G., British Patent 598,536 (1948); *C. A.*, **42**, 6379 (1948).

[282] Geigy, A.-G., Swiss Patent 251,296 (1948); *C. A.*, **43**, 7962 (1949).

[283] Geigy, A.-G., Swiss Patent 253,173 (1948); *C. A.*, **44**, 1537 (1950).

[284] Geigy, A.-G., British Patent 598,472 (1948); *C. A.*, **42**, 6851 (1948).

[285] Kolloff and Hunter, *J. Am. Chem. Soc.*, **62**, 1646 (1940).

[286] Mousseron, Winternitz, Martin-Peridier and Vincent, *Trav. soc. pharm. Montpellier*, **6**, 38 (1946–47); *C. A.*, **43**, 1028 (1949).

[287] Rajagopalan, *Proc. Indian Acad. Sci.*, **19, A**, 343 (1944); *C. A.*, **39**, 508 (1945).

[288] Adkins and Wojcik, *J. Am. Chem. Soc.*, **56**, 247 (1934).

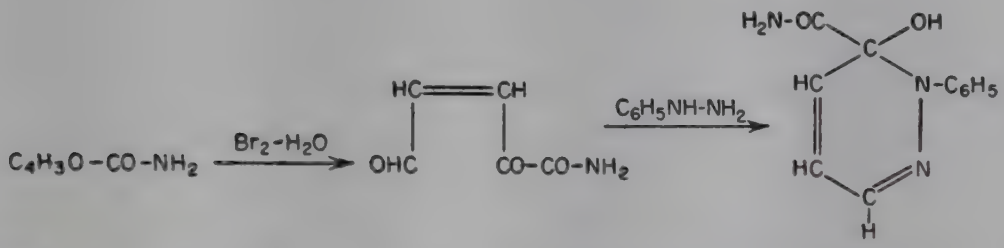
[289] Wojcik and Adkins, *J. Am. Chem. Soc.*, **56**, 2419 (1934).

[290] Bogert and Stull, *J. Am. Chem. Soc.*, **49**, 2011 (1927).

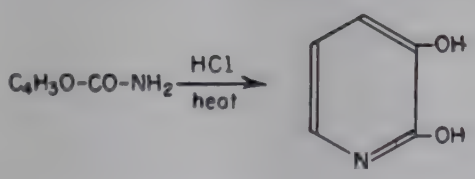
[291] Bogert and Stull, *J. Am. Chem. Soc.*, **47**, 3078 (1925).

pentachloride, no doubt by way of the intermediate chloride, $C_4H_3O—CCl_2—NH_2$, although this compound has not been isolated. However, from N-ethyl-2-furamide, Wallach[254] isolated a product analyzing correctly for such a chloride.

At low temperature with dry bromine, 2-furamide forms a tetrabromo addition product (see p. 108). With aqueous bromine, it dissolves to give a colorless solution, changing to dark blue or purple upon addition of an inorganic base. When aniline is substituted for the latter, a reddish precipitate of unknown constitution is formed. On the other hand, phenylhydrazine gives a brilliant red, amorphous material, $C_{11}H_{11}N_3O_2$.[292] The identity of this product was not ascertained, but in view of the ready formation of 1,4-dicarbonyl compounds by oxidation of furans (see Chapter 14), it is not unlikely that the compound in question is the substituted dihydropyridazine shown below:



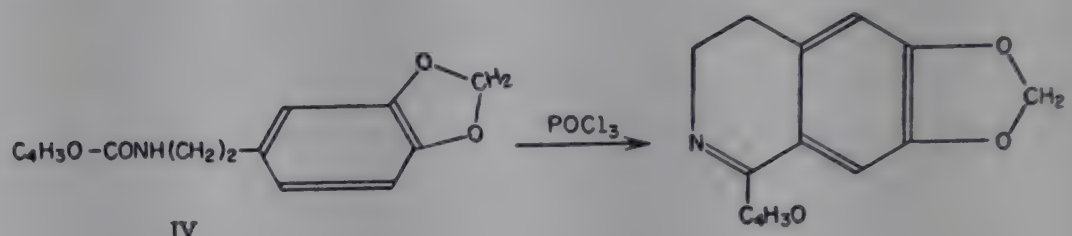
Aso[293] has reported the formation of 2,3-dihydroxypyridine as one of the products obtained on heating 2-furamide with hydrochloric acid at 155–160° for several hours. A similar ring expansion was noted with the homologous 5-methyl-2-furamide which gave rise to 5-methyl-2,3-dihydroxypyridine. These same products were also obtained by heating the aldehydes (furfural and 5-methylfurfural, respectively) with hydroxylammonium chloride (see also Chapter 14).



Raman[294] obtained N-homopiperonyl-2-furamide, IV, by the action of homopiperonylamine on ethyl 2-furoate. The product which was not purified, was refluxed with phosphorus oxychloride in toluene, and under these conditions, cyclodehydration took place with the formation of the substituted isoquinoline, V (m.p. 95–96°). It is interesting to observe that the related amides derived from 3-(2-furyl)propionic and 3-(5-phenyl-2-furyl)-propionic esters and homopiperonylamine did not cyclize to the correspond-

[292] Saunders, *Am. Chem. J.*, **15**, 130 (1893).
[293] Aso, *J. Agr. Chem. Soc. Japan*, **16**, 253 (1940); *C. A.*, **34**, 6940 (1940).
[294] Raman, *J. Indian Chem. Soc.*, **17**, 715 (1940); *C. A.*, **35**, 6593 (1941).

ing isoquinolines,[294] although the homoveratrylamide of the former acid was successfully cyclized by Harwood and Johnson.[295]



IV V

2-Furoylthiourea Derivatives

The furoylureas are unknown, but a number of 2-furoylthiourea derivatives, VII, have been described by Douglass and Dains.[227] These were synthesized from 2-furoyl isothiocyanate by combination with a variety of amines. Yields were in the neighborhood of 70–80 per cent with arylamines, but lower with alkylamines. The furoyl isothiocyanate, VI, was not isolated, being formed, in acetone solution, from 2-furoyl chloride and ammonium thiocyanate. The solution was used directly to obtain the thiourea derivatives listed in Table 9.

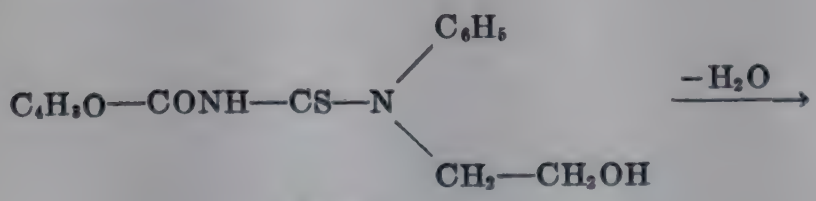
$$C_4H_3O\text{—}COCl \xrightarrow{NH_4SCN} C_4H_3O\text{—}CO\text{—}NCS \xrightarrow{RNH_2}$$

VI

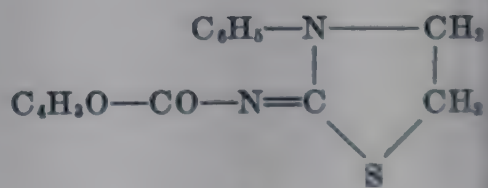
$$C_4H_3O\text{—}CONH\text{—}CS\text{—}NHR$$

VII

With phenylaminoethanol, the isothiocyanate yielded N-2-furoyl-N′-(2-hydroxyethyl)-N′-phenylthiourea, VIII, which, on treatment with strong sulfuric acid, cyclized to give 2-(2-furoylimino)-3-phenylthiazolidine, IX, melting at 123°.



VIII



IX

[295] Harwood and Johnson, *J. Am. Chem. Soc.*, **55**, 2555 (1933).

TABLE 9. FUROYLTHIOUREAS[227]

Compound	M.p. (°C.)
N-2-furoyl-N′-methylthiourea	142
N-2-furoyl-N′-ethylthiourea	101–102
N-2-furoyl-N′-benzylthiourea	122
N-2-furoyl-N′-phenylthiourea	116
N-2-furoyl-N′-*o*-tolylthiourea	115–116
N-2-furoyl-N′-*m*-tolylthiourea	99
N-2-furoyl-N′-*p*-tolylthiourea	130
N-2-furoyl-N′-α-naphthylthiourea	139–140
N-2-furoyl-N′-β-naphthylthiourea	139–140
N-2-furoyl-N′-(2-hydroxyethyl)-N′-phenylthiourea	111
N-2-furoyl-N′-benzyl-N′-phenylthiourea	124
N-2-furoyl-N′-diphenylthiourea	139–140

2-Furamido Carboxylic Acids

N-2-furoylglycine (pyromycuric acid), X, was found by Jaffe and Cohn[296] in the urine of animals (dog and rabbit) which had been fed furfural. 2-Furoic acid is likewise eliminated from the human body in this form.[297] The same compound was synthesized by Baum[170] (see also [298]) by furoylation of glycine with 2-furoyl chloride. The other furamido acids listed below were derived similarly, with the exception of N,N′-di-2-furoylornithine, which was isolated from the excrement of chickens which had been given furfural.

$$C_4H_3O—COCl + H_2NCH_2COOH \rightarrow \underset{X}{C_4H_3O—CONHCH_2COOH}$$

N-2-furoylglycine: (2-furamidoacetic acid) $C_4H_3O—CONHCH_2COOH$, prisms, m.p. 165°, in 82 per cent yield. Difficultly soluble in alcohol; 1 part soluble in 31.5 parts water at 20.5°. For enzymatic hydrolysis, see Utjino *et al.*[299] **Ethyl ester,** m.p. 77°; easily soluble in alcohol, ether and benzene; 1 part soluble in 43.3 parts of water at 17.5°.[170]

N-2-furoylalanine: (α-2-furamidopropionic acid) $C_4H_3O—CONHCH(CH_3)COOH$, six-sided, shiny tablets, m.p. 169°; in practically quantitative yield. Insoluble in ligroin and ether and very difficultly soluble in cold alcohol. At 14°, 1 part dissolves in 121.4 parts of water. Barium salt, microcrystalline. Silver salt, forms white, four-sided, light-sensitive prisms, difficultly soluble in cold alcohol. **Ethyl ester,** m.p. 71–72°; crystallizes from water in small six-sided prisms; easily soluble in alcohol, ether and benzene and more difficultly in ligroin; 1 part soluble in 60.1 parts of water at 17°. Baum was unsuccessful in attempting to resolve N-2-furoylalanine, by means of brucine, into its *d*- and *l*-components.[170]

[296] Jaffe and Cohn, *Ber.*, **20,** 2311 (1887).
[297] Schempp, *Z. physiol. Chem.*, **117,** 41 (1921).
[298] Sasaki, *Biochem. Z.*, **25,** 272 (1910); *C. A.*, **4,** 2004 (1910).
[299] Utjino, Tsunoo and Mori, *J. Biochem. Japan*, **26,** 449, 477 (1937); *C. A.*, **32,** 2156–7 (1938).

α-2-Furamidophenylacetic acid: C_4H_3O—CONHCH(C_6H_5)COOH, white needles, m.p. 178–179°. Difficultly soluble in cold water (1 part in 713 parts at 17°), easily soluble in alcohol, ether, benzene and chloroform. With barium carbonate, the barium salt was obtained as a gelatinous crust, which on trituration with alcohol changes to three-cornered prisms.[170]

N-2-furoylaspartic acid: (2-furamidosuccinic acid)

$$C_4H_3O—CONHCH(COOH)CH_2COOH$$

four-sided prisms (from water), m.p. 162–163°, in 60 per cent yield. Easily soluble in alcohol, difficultly in ether and in benzene; 1 part soluble in 11.25 parts of water at 19.5°; $[\alpha]_D^{20} = +43.17°$. Barium salt insoluble in alcohol, soluble in water.[170]

N-2-furoylasparagine: C_4H_3O—CONHCH(COOH)CH_2CONH_2, colorless, four-cornered prisms (from water), m.p. 172–173°, in 96 per cent yield. Insoluble in alcohol, ether and ligroin; 1 part soluble in 93.7 parts of water at 16°; $[\alpha]_D^{20} = +19.75°$. Barium, copper, silver and lead salts prepared.[170]

N-N′-di-2-furoylornithine: C_4H_3O—$CONH(CH_2)_3CH(NHCO—C_4H_3O)COOH$, m.p. 186°.[300]

Furamido Compounds as Dyestuffs

Kizhner and Krasova[270] prepared several derivatives of *p*-aminofuranilide (see Table 6), and found that they behaved like the corresponding aminobenzanilides (Fast Violet B type dyes) with respect to color and fastness. Related products are described by Etzelmiller,[269] who cites their suitability for use in the production of water-insoluble dyes and pigments, and their diazotization and coupling with ice color components to give attractive hues of excellent fastness. The general synthesis involves condensation of the appropriately substituted nitroaniline with 2-furoyl chloride, and subsequent reduction of the nitro group as indicated below.

$$C_4H_3O—COCl + H_2NC_6H_4(NO_2)\text{-}p \rightarrow$$
$$C_4H_3O—CONHC_6H_4(NO_2)\text{-}p \rightarrow C_4H_3O—CONHC_6H_4(NH_2)\text{-}p$$

The synthesis of a number of Algol type anthraquinone dyes in which a 2-furoyl group is substituted for benzoyl is reported by Mangini *et al.*[301, 302, 303] The compounds tabulated below (Table 10) were derived from the appropriate aminoanthraquinones by furoylation with 2-furoyl chloride in nitrobenzene. Comparison with the corresponding benzamidoanthraquinone derivatives indicated similar spectroscopic and dyeing properties.

2-Furamidines. Unsubstituted 2-furamidine has not been reported in the free form. However, Pinner[304] isolated the hydrochloride, II (m.p. 72°) by the action of alcoholic ammonia on the corresponding salt, I, of ethyl

[300] Jaffe and Cohn, *Ber.*, **21**, 3461 (1888).

[301] Mangini and Weger, *Boll. soc. facoltà chim. ind. Bologna*, **3**, 223, 232 (1942); *C. A.*, **39**, 417–19 (1945).

[302] Mangini and Nicolini, *Boll. soc. facoltà chim. ind. Bologna*, **4**, 1 (1943); *C. A.*, **40**, 7634 (1946).

[303] Mangini and Dal Monte, *Boll. soc. facoltà chim. ind. Bologna*, **4**, 8 (1943); *C. A.*, **40**, 7634 (1946).

[304] Pinner, *Ber.*, **25**, 1414 (1892).

TABLE 10. ALGOL DYE BASES CONTAINING THE FURAN NUCLEUS[301, 302, 303]

Substituted anthraquinone	M.p. (°C.)	Appearance
1-(2-Furamido)-	275–276	yellow needles or orange prisms
1,5-Di(2-furamido)-	350	yellow-brown needles
1,8-Di(2-furamido)-	345	orange-yellow needles
1-(2-Furamido)-4-hydroxy-	273	red plates or needles
1,5-Di(2-furamido)-	>350	red needles
1-(2-Furamido)-2-bromo-	232–233	green plates
1-(2-Furamido)-2-bromo-4-*p*-toluidino-	259	deep violet needles
1-(2-Furamido)-2-bromo-4-*p*-phenetidino-	267–268	violet needles
1-(2-Furamido)-2-bromo-4-diphenylamino-	259	blue-violet needles
1-(2-Furamido)-2-bromo-4-α-naphthylamino-	227–228	violet needles
1-(2-Furamido)-2-bromo-4-β-naphthylamino-	242	violet needles
1,5-Di(2-furamido)-2,6-dibromo-4,8-dianilino-	263	all violet or blue-violet
1,8-Di(2-furamido)-2,7-dibromo-4,5-dianilino-	165	
1,5-Di(2-furamido)-2,6-dibromo-4,8-di-*p*-toluidino-	285	
1,8-Di(2-furamido)-2,7-dibromo-4,5-di-*p*-toluidino-	192–193	
1,5-Di(2-furamido)-2,6-dibromo-4,8-di-*p*-anisidino-	265	
1,8-Di(2-furamido)-2,7-dibromo-4,5-di-*p*-anisidino-	173–175	
1,5-Di(2-furamido)-2,6-dibromo-4,8-di-*p*-phenetidino-	259	
1,8-Di(2-furamido)-2,7-dibromo-4,5-di-*p*-phenetidino-	172–173	

2-furimidate. He was unsuccessful in attempting to free the amidine from the salt form, 2-furamide being formed instead.

$$\underset{\text{I}}{C_4H_3O{-}C(NH)OC_2H_5\cdot HCl} \xrightarrow{NH_3} \underset{\text{II}}{C_4H_3O{-}C(NH)NH_2\cdot HCl}$$

A number of N-alkyl-N′-aryl-2-furamidines, III, were synthesized by Degnan and Pope[265] (see also [305]) in an extension of the work which has been carried out on physiologically active amidines. The procedure involved interaction of the appropriate N-alkyl-2-furamide[1] with phosphorus penta-

[1] It is interesting to note that it was not possible to reverse this procedure and use N-aryl-2-furamides and aliphatic amines as the starting materials.[265]

[305] Takahashi, Saikachi, Kimura and Yoshina, *J. Pharm. Soc. Japan*, **68**, 42 (1948); *C. A.*, **44**, 1954 (1950).

chloride in benzene solution, after which the reaction mixture was boiled with an aromatic amine. The course of reaction is indicated below as occurring via the intermediate furimidyl chlorides, although these were not isolated.

$$C_4H_3O\text{—}CONHR \xrightarrow{PCl_5} [C_4H_3O\text{—}C(Cl)\text{=}NR] \xrightarrow{R'NH_2} C_4H_3O\text{—}C(NR)NHR'$$

III

Table 11. Some N,N′-disubstituted 2-Furamidines

Substituents	M.p., °C.	Hydrochloride, m.p., °C.	Ref.
N-propyl-N′-phenyl	63.5–64	139–140	265
N-butyl-N′-phenyl	67–68	141–142	265
N-cyclohexyl-N′-phenyl	78.5–79	174	265
N-allyl-N′-*p*-methoxyphenyl	65–66	—	305
N-allyl-N′-*p*-ethoxyphenyl	b.p. 210–216 (2 mm.)	—	305
N-propyl-N′-*p*-ethoxyphenyl	81–81.5	78.5–79.5 (+1 H_2O)	265
N-butyl-N′-*p*-ethoxyphenyl	65.5–66	135–136	265
N-2-butyl-N′-*p*-ethoxyphenyl	52–52.5	132–133	265
N-pentyl-N′-*p*-ethoxyphenyl	61.0–61.5	75–76 (+1 H_2O)	265
N-2-pentyl-N′-*p*-ethoxyphenyl	75–76	125.5–126.5	265
N-(3-methyl-1-butyl)-N′-*p*-ethoxyphenyl	78–79	142–143	265
N-(4-methyl-2-pentyl)-N′-*p*-ethoxyphenyl	77	120–121	265
N-cyclohexyl-N′-*p*-ethoxyphenyl	108–109	170–171	265
N-propyl-N′-*p*-carbethoxyphenyl	86–87	167–168	265
N-butyl-N′-*p*-carbethoxyphenyl	75.5–76	128–129	265
N-cyclohexyl-N′-*p*-carbethoxyphenyl	114–115	188–189	265
N-butyl-N′-α-naphthyl	54.5–55.5	99–101	265
N-butyl-N′-β-naphthyl	61.6–62	91.5–92.5	265
N-ethyl-N′-3-pyridyl	b.p. 126–128 (8 mm.)	—	305
N-allyl-N′-3-pyridyl	b.p. 130–135 (4 mm.)	—	305
N-allyl-N′-(4-methyl-2-thiazolyl)	b.p. 110–115 (2 mm.)	—	305

A pharmacological evaluation of these furamidine hydrochlorides showed that those of the N-alkyl-N′-*p*-phenetyl- series exhibited a high persistency of anesthetic action coupled with moderate toxicity. The maximum persistency was attained with *n*-butyl as the alkyl radical, this particular

furamidine being more than three times as active as cocaine. The derivatives with a *p*-carbethoxyphenyl radical were found to be highly irritating; they precipitated on topical application to rabbits' eyes. Compounds possessing the phenyl or naphthyl groups showed poor anesthetic properties.[265]

N-sulfanilyl-2-furamidine, IV, is described in a patented disclosure.[280] This derivative, which melts at 165–166°, is converted into N-*p*-amino-sulfanilyl-2-furamide, V, on heating with dilute hydrochloric acid.

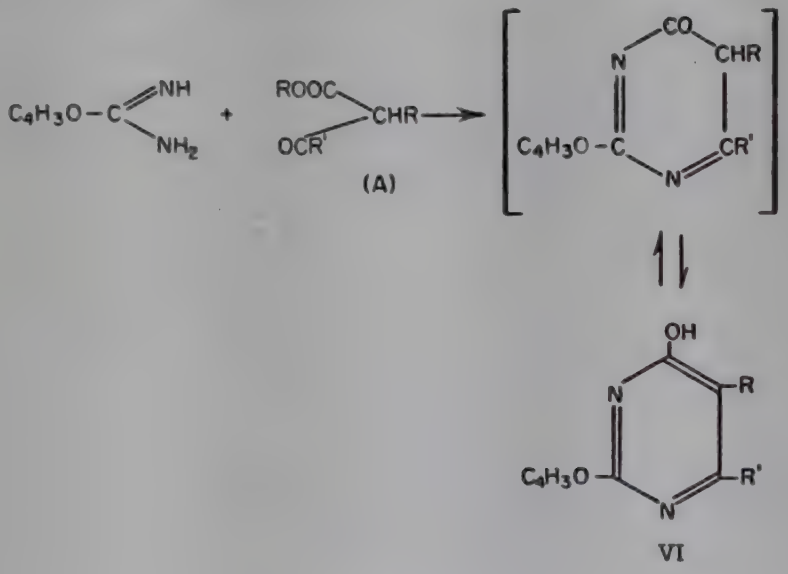
$$C_4H_3O—C(NH)NH—SO_2C_6H_4(NH_2)\text{-}p \xrightarrow{\text{dil. HCl}}$$

IV

$$C_4H_3O—CONH—SO_2C_6H_4(NH_2)\text{-}p$$

V

Like its benzene analog, 2-furamidine (employed as the hydrochloride in alkali) condenses with compounds possessing the grouping —CO—CHR—CO— with the formation of substituted pyrimidines, VI. Several of these derivatives have been prepared as indicated below (see also [306, 307]).



VI

[2-(2-furyl)-4-hydroxy-5-R-6-R-pyrimidine]

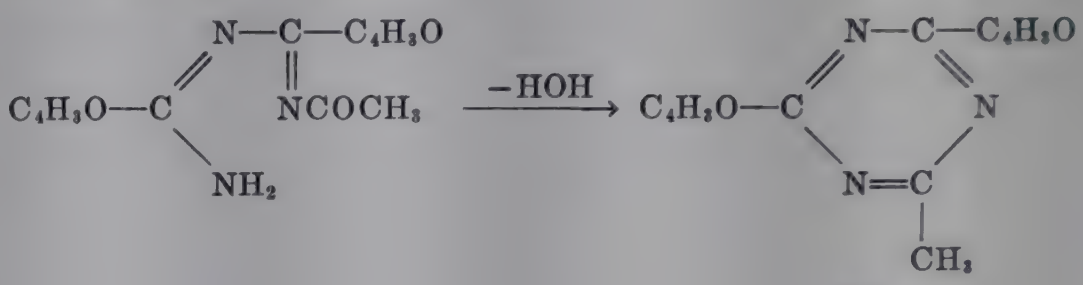
Reactant A	Product VI (m.p., °C.)	Ref.
Acetoacetic ester	R = H; R′ = CH_3 (225)	304
Benzoylacetic ester	R = H; R′ = C_6H_5 (256)	304
Methylacetoacetic ester	R = CH_3; R′ = CH_3 (231)	304
Benzylacetoacetic ester	R = $C_6H_5CH_2$; R′ = CH_3 (238)	304
α-Formylphenylacetic ester	R = C_6H_5; R′ = H (222–223)	308
Oxaloacetic ester*	R = H; R′ = COOH (>300, dec.)	304

* It was possible in this reaction to isolate the intermediate condensation product, $C_4H_3O—C(NH)NH—COCH_2CO—COOC_2H_5$, m.p. 190° (dec.).[304]

[306] Pinner, *Ber.*, **26**, 2122 (1893).
[307] Pinner, *Ber.*, **28**, 473 (1895).
[308] Davies and Piggot, *J. Chem. Soc.*, **1945**, 347.

When 2-furamidine was refluxed with acetic anhydride, there was obtained a crystalline compound, $C_{12}H_9N_3O_2$, m.p. 138°. On account of its weak basicity, Pinner[304] concluded that this product was not the expected difuryl-aminopyrimidine (by analogy with the behavior of acetamidine), and postulated the triazine structure, VII (2,4-difuryl-6-methyl-1,3,5-triazine), formed as shown below. Similarly, Pinner reports 2,4-difuryl-6-hydroxy-1,3,5-triazine, m.p. 250°, by condensation of furamidine with phosgene.

$$2\ C_4H_3O{-}C(NH)NH_2 + (CH_3CO)_2O \rightarrow$$



VII

2-Furohydroxamic Acid and Its Derivatives. 2-Furohydroxamic acid, I, is obtained by the action of an alcoholic solution of hydroxylamine on 2-furoic ester.[309, 310, 158] N-acyloxy derivatives, II, are formed in the usual manner by treatment of I with acid chlorides or anhydrides.

$$C_4H_3O{-}COOR \xrightarrow{NH_2OH} \underset{\text{I}}{C_4H_3O{-}CONHOH} \xrightarrow{RCOCl} \underset{\text{II}}{C_4H_3O{-}CONHOCOR}$$

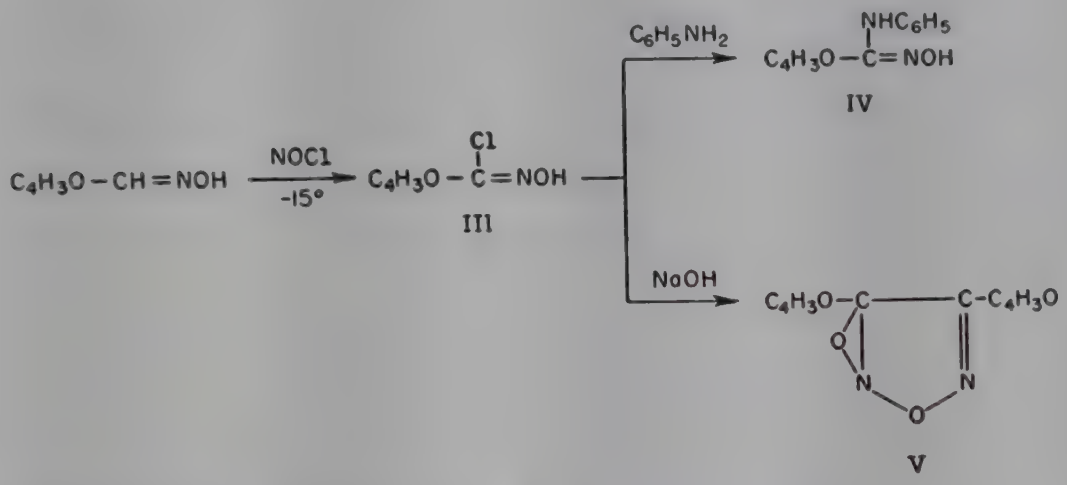
Pickard and Neville[309] had hoped to synthesize *sym.*-difurylurea from the benzoyl ester (II, R = C_6H_5) by hydrolytic rearrangement of the sodium salt of the latter. When this was attempted, carbon dioxide was liberated as expected, but the product was a resinous material which could not be crystallized. Jones and Hurd[310] reported essentially similar results. In the same way, alcoholysis of the sodium salt with the object of preparing 2-furylurethan resulted in failure.[309] I is decomposed by fuming nitric acid even at 0°.[158]

2-Furohydroxamic acid: m.p. 124°, 119–122°; lustrous needles from water; gives the expected cherry-red color with ferric chloride; soluble in alcohol, water, ethyl acetate; insoluble in ether, chloroform, carbon disulfide, ligroin, benzene.[309, 310] **Acetyl ester,** m.p. 95–96°; from the acid and acetic anhydride[310] or ketene[311]; **diacetyl**

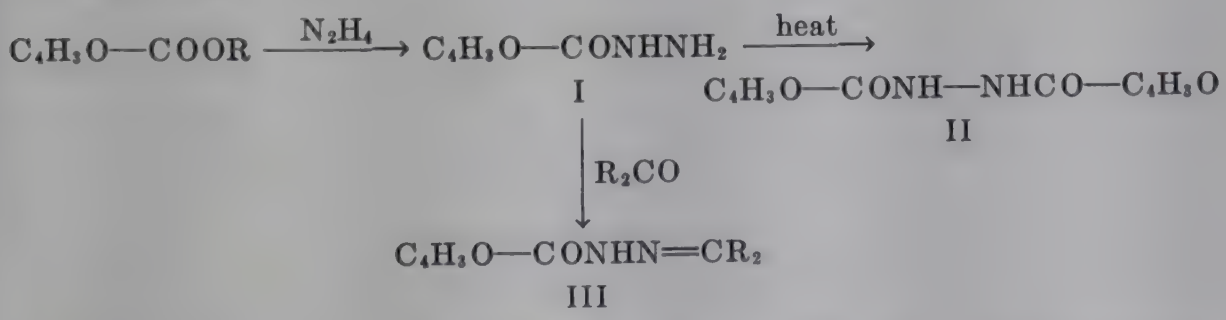
[309] Pickard and Neville, *J. Chem. Soc.*, **79,** 847 (1901).
[310] Jones and Hurd, *J. Am. Chem. Soc.*, **43,** 2422 (1921).

ester, m.p. 54–55°; from the acid and an excess of ketene[311]; **benzoyl ester,** m.p. 140°; from the acid and benzoyl chloride.[310] Pickard and Neville[309] give the m.p. as 134°; **2-furoyl ester** (di-2-furohydroxamic acid), m.p. 180°.[170]

The action of nitrosyl chloride on furfural oxime results in the formation of 2-furohydroxamyl chloride, III, melting at 103–104°.[312] With aniline, the chloride reacts to give 2-furanilidoxime, IV (m.p. 126–127°), which gives an emerald-green color with ferric chloride. When shaken with sodium hydroxide, III loses hydrogen chloride, presumably with the formation of 2-furonitrile oxide, although under the conditions employed, the product isolated from the reaction mixture was the polymer, difurylfuroxan, V (m.p. 113–114°).



Hydrazides and Hydrazidines. The furoic hydrazides are obtained in the usual manner by interaction of 2-furoic ester with hydrazine or its derivatives. With hydrazine itself the monoacyl derivative (I) is formed, which when heated alone or with iodine is converted into the *sym.*-diacylhydrazine, II. Condensation of I with aldehydes and ketones proceeds by elimination of water to give III.



2-Furohydrazide: $C_4H_3O—CONHNH_2$; m.p. 80°, b.p. 279° (dec.); only slightly soluble in the common solvents; **hydrochloride,** m.p. 178°[152] (see also [263]).

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[311] Hurd and Cochran, *J. Am. Chem. Soc.*, **45,** 515 (1923).
[312] Rheinboldt, Dewald, Jansen and Schmitz-Dumont, *Ann.*, **451,** 161 (1926).

Some substituted furohydrazides[314]

	M.p. (°C.)
5-methyl-2-	61–62
5-bromo-2-	135.5–136
2-methyl-3-	149.5–150
2,4-dimethyl-3-	144–145
2,5-dimethyl-3-	136–136.3

***Sym.*-di(2-furoyl)hydrazine:** $C_4H_3O—CONHNHCO—C_4H_3O$; m.p. 232°; soluble in hot alcohol, in chloroform and slightly soluble in hot benzene.[152]

α-2-Furoyl-β-acetylhydrazine: $C_4H_3O—CONHNHCOCH_3$; m.p. 153.5°; from 2-furohydrazide and acetic anhydride.[152]

α-2-Furoyl-β-benzoylhydrazine: $C_4H_3O—CONHNHCOC_6H_5$; m.p. 226°; from 2-furohydrazide and benzoyl chloride.[152]

2-Furo(benzylidenehydrazide): $C_4H_3O—CONHN=CHC_6H_5$; m.p. 219° (dec.); from 2-furohydrazide and benzaldehyde.[152]

2-Furo(isopropylidenehydrazide): $C_4H_3O—CONHN=C(CH_3)_2$; m.p. 72°; from 2-furohydrazide and acetone.[152]

2-Furo(carbethoxyisopropylidenehydrazide):

$$C_4H_3O—CONHN=C(CH_3)CH_2COOC_2H_5$$

m.p. 234°; from 2-furohydrazide and acetoacetic ester.[152]

2-Furophenylhydrazide: $C_4H_3O—CONHNHC_6H_5$; m.p. 144°; from 2-furoyl chloride and phenylhydrazine. At 17°, 1 part dissolves in 27.8 parts of alcohol[170] (see also [232, 7]).

2-Furo(2,4-dinitrophenylhydrazide): $C_4H_3O—CONHNHC_6H_3(NO_2)_2$; m.p. 211–212°.[313]

N-2-furoyl-N′-methyl-N′-2,4-dinitrophenylhydrazine:

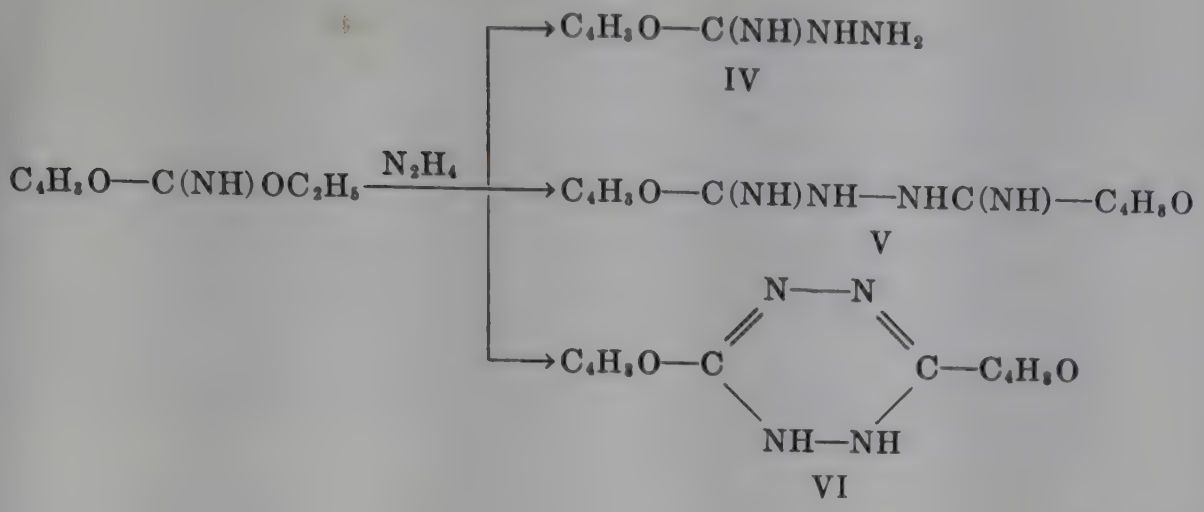
$$C_4H_3O—CONH—N(CH_3)C_6H_3(NO_2)_2;\ \text{m.p. } 177–179°.[313]$$

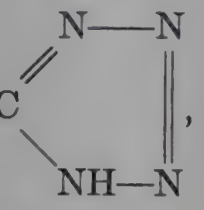
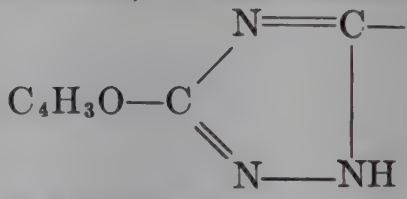
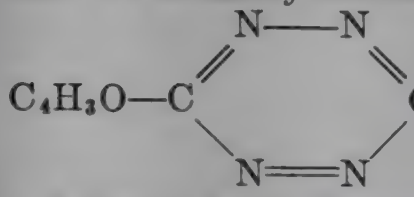
N,N′-di-2-furoyl-N-2,4-dinitrophenylhydrazine:

$$C_4H_3O—CONH—N(OC—C_4H_3O)C_6H_3(NO_2)_2;\ \text{m.p. } 195–197°.[313]$$

Pinner and Caro[315] studied the formation of the mono- and di-2-furohydrazidines, and the heterocyclic nitrogen compounds resulting by cyclization of these products. They demonstrated that reaction of hydrazine with ethyl 2-furimidate follows a course similar to that observed with aromatic analogs. In the reaction mixture they found, not only the expected hydrazidine, IV (picrate, m.p. 164°; benzylidene derivative, m.p. 142°), but also di-2-furohydrazidine, V (m.p. 185°), and di-2-furyldihydrotetrazine, VI (m.p. 208°; diacetyl derivative, m.p. 197°).

[313] Bredereck and Fritzsche, *Ber.*, **70**, 802 (1937).
[314] Blomquist and Stevenson, *J. Am. Chem. Soc.*, **56**, 146 (1934).
[315] Pinner and Caro, *Ber.*, **28**, 465 (1895).



With nitrous acid, IV gives rise to C-2-furyltetrazole,  , m. p. 199° (dec.). On treatment with acids, V loses ammonia with formation of the di-2-furyltriazole,  , m.p. 185°. VI is readily oxidized in air to di-2-furyltetrazine,  , m.p. 195°.

2-Furoyl Azide. Treatment of 2-furoic hydrazide with sodium nitrite in acetic acid gives 2-furoyl azide in 66 per cent yield.[153] The product is a white, crystalline material, easily soluble in alcohol, ether, chloroform, ligroin and benzene. It attacks the mucous membrane strongly.[152]

$$C_4H_3O—CONH—NH_2 \xrightarrow[AcOH]{NaNO_2} C_4H_3O—CON_3$$

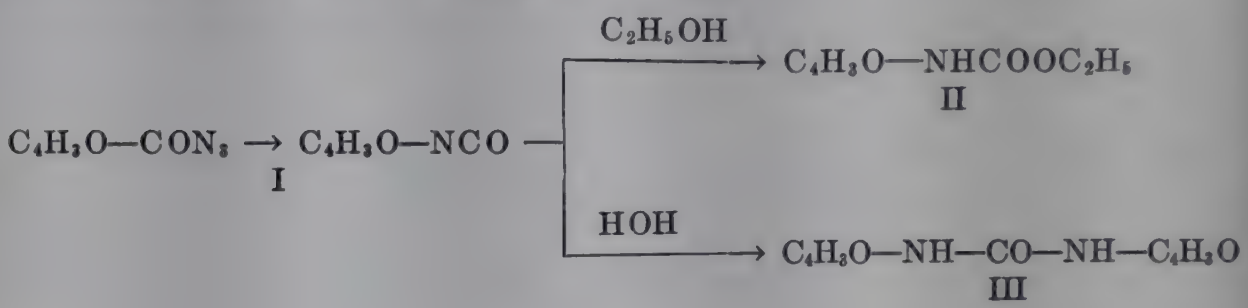
Freundler[263] was the first to carry out this transformation, and he reported the melting point of the azide as 90°. Later, Curtius and Leimbach[152] repeated the preparation, and give the melting point as 65.5°, which checks reasonably closely with melting point 62.5°, found by Marquis.[153]

The azide has also been synthesized in 92 per cent yield from 2-furoyl chloride by the action of sodium azide in ether.[316]

[316] Singleton and Edwards, *J. Am. Chem. Soc.*, **60**, 540 (1938).

Decomposition of the azide proceeds normally by cautious heating in a suitable solvent to give 2-furyl isocyanate, I.[316, 314] In the absence of a solvent, however, the azide explodes violently on heating,[314] although this difficulty may be minimized by decomposing successive small portions, so that in essence, the isocyanate which is formed acts as the solvent medium.[317]

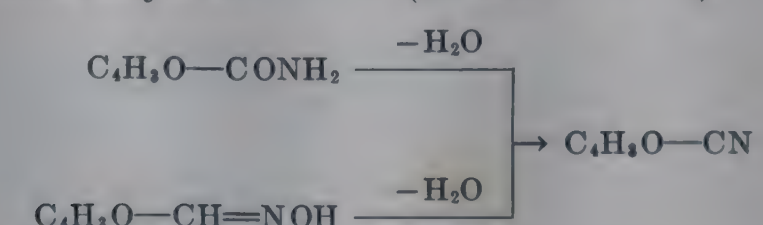
On boiling with alcohol, 2-furoyl azide yields 2-furylurethan, II, from which Freundler,[263] Curtius and Leimbach,[152] and Marquis[153] all attempted, unsuccessfully, to obtain 2-furylamine by hydrolysis (see p. 183). Di-2-furylurea, III, is formed in traces by warming the azide with water or, in somewhat better yield, by using wet benzene.[152]



Some substituted furoyl azides[314]

	M.p. (°C.)
5-methyl-2-furoyl-	35–36
5-bromo-2-furoyl-	66–67
2-methyl-3-furoyl-	22–23
2,4-dimethyl-3-furoyl-	liquid
2,5-dimethyl-3-furoyl-	24–25

2-Furonitrile. Apparently Wallach[318, 254] was the first to prepare 2-furonitrile. His method was warming 2-furamide with phosphorus pentachloride which, in the hands of Gilman and Hewlett,[228] gave the nitrile in 70 per cent yield. A short time later, Ciamician and Dennstedt[253, 319] reported obtaining the nitrile in 51 per cent yield by distillation of the amide over phosphorus pentoxide. It has also been obtained by dehydration of furfural oxime with acetic anhydride[242, 304, 320] (see also [321, 322, 323]).



[317] Stevenson and Johnson, *J. Am. Chem. Soc.*, **59**, 2525 (1937).
[318] Wallach, *Ber.*, **14**, 751 (1881).
[319] Ciamician and Dennstedt, *Gazz. chim. ital.*, **11**, 293 (1881).
[320] Reichstein, Grüssner and Zschokke, *Helv. Chim. Acta*, **15**, 1066 (1932).
[321] Minunni and Vassallo, *Gazz. chim. ital.*, **26, I**, 463 (1896).

More recently,[324] a process for the production of 2-furonitrile has been described in which furoic acid vapors in admixture with an excess of ammonia are brought into contact with a phosphated-alumina dehydration catalyst at 275–375°.

TABLE 12. NITRILES OF SOME 2-FURANCARBOXYLIC ACIDS

Compound	Physical constants (°C.)	Ref.
2-Furonitrile	b.p. 146 (738 mm.); d_4^{20} 1.0822	318, 254, 253, 319, 242, 228, 155, 320
5-Methyl-2-furonitrile	b.p. 65–67 (15 mm.), 74–75 (21 mm.) d_4^{20} 1.0399, d_4^{25} 1.0348; n_D^{20} 1.4848	325, 326, 327, 328
5-Ethyl-2-furonitrile	b.p. 68–70 (vac.)	329
3-Methyl-2-furonitrile (Elsholtzia nitrile)	b.p. 54.5–55 (12 mm.)	330, 331
4-Methyl-2-furonitrile	b.p. 57–58 (12 mm.)	332; see also 333
4,5-Dimethyl-2-furonitrile	b.p. 77–78 (11 mm.)	334

2-Furonitrile (2-furyl cyanide) is a colorless liquid which boils at 147°. It is heavier than water, and discolors on standing in contact with air. Ciamician and Dennstedt[253, 319] observed its sweetness in taste, which property was later quantitated by Gilman and Hewlett[228] who reported it to be 100 times as sweet as cane sugar, and only half as sweet as 3-(2-furyl)acrylonitrile.

In common with other nitriles, 2-furonitrile participates in many additive reactions involving the C≡N group. Thus, reduction with zinc and sulfuric acid gives 2-furfurylamine, $C_4H_3O—CH_2NH_2$.[318, 254, 253, 319] Under these conditions the yield of amine is very poor, whereas on hydrogenation of the nitrile over Raney nickel at room temperature, the amine is produced in 84 per cent yield along with 11 per cent of di-2-furfurylamine.[335]

[322] Borsche, *Ber.*, **39**, 2503 (1906).
[323] Obregia and Gheorghiu, *J. prakt. Chem.*, **128**, 239 (1930).
[324] Howk and Wortz, (to E. I. du Pont de Nemours & Co.), U. S. Patent 2,195,966 (1940); *C. A.*, **34**, 5095 (1940).
[325] Runde, Scott and Johnson, *J. Am. Chem. Soc.*, **52**, 1284 (1930).
[326] Reichstein, *Ber.*, **63**, 749 (1930).
[327] Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).
[328] Eliel and Peckham, *J. Am. Chem. Soc.*, **72**, 1209 (1950).
[329] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 1124 (1932).
[330] Reichstein, Zschokke and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).
[331] Sherman and Amstutz, *J. Am. Chem. Soc.*, **72**, 2195 (1950).
[332] Reichstein and Zschokke, *Helv. Chim. Acta*, **14**, 1270 (1931).
[333] Rinkes, *Rec. trav. chim.*, **50**, 1127 (1931).
[334] Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 28 (1933).
[335] Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).

Treatment of 2-furonitrile with hydrogen sulfide in alcoholic ammonia gives 2-thiofuramide, $C_4H_3O—CS—NH_2$.[242]

Ketones are formed on hydrolysis of the products obtained by the addition of organomagnesium halides to 2-furonitrile.[320, 336, 337] Thus, phenylmagnesium bromide gives rise to 2-furyl phenyl ketone in 70 per cent yield,

$$C_4H_3O—CN \xrightarrow{RMgX} \xrightarrow{HOH} C_4H_3O—COR$$

the reaction proceeding at an unusually high rate as shown by Gilman and Lichtenwalter[336] who compared the rates of reaction of a variety of nitriles with this Grignard reagent.

Derivatives of the enol form of 2-furamide, the furimidic esters, I, are formed (as the hydrochlorides) by treating an alcoholic solution of the nitrile with hydrochloric acid.

$$C_4H_3O—CN \xrightarrow[HCl]{ROH} C_4H_3O—C(NH)OR$$

I

Methyl 2-furimidate: (2-furimidic methyl ester); $C_4H_3O—C(NH)OCH_3$, a colorless liquid, b.p. 169–172°. On heating the imido ester with methyl iodide, it rearranges to the isomeric N-methyl-2-furamide.[264]

Ethyl 2-furimidate: $C_4H_3O—C(NH)OC_2H_5$; b.p. 180–181°; **hydrochloride,** m.p. 106° (dec.).[304, 315]

Nuclear Substituted 2-Furoic Acids

The material to be discussed in this section includes all nuclear substituted 2-furancarboxylic acids with the exception of the nitro-acids (p. 157), the halogen substituted acids (p. 106), and the sulfofuroic acids (p. 509). For convenience, the furan acids possessing an amino or substituted amino group directly attached to the nucleus are also treated elsewhere (p. 188).

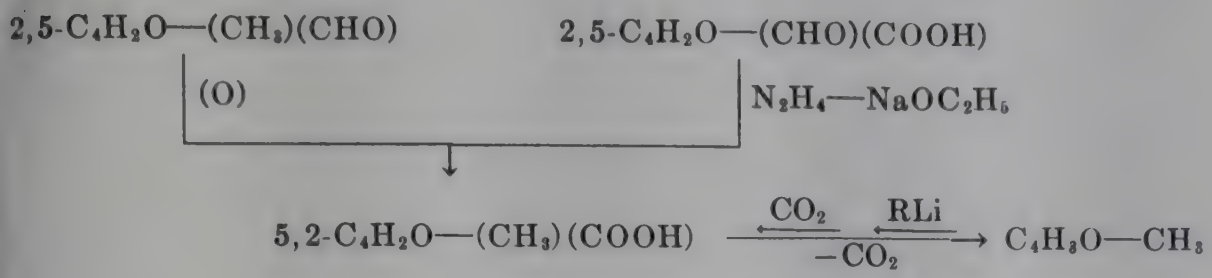
Alkyl-2-furoic Acids and Related Acids

Theoretically, there are six isomeric mono-alkyl-furanmonocarboxylic acids. That is, a particular alkyl substituent may occupy any one of three nuclear positions when the carboxyl group is located either alpha or beta. The only complete series of this type which is known is that in which the alkyl radical is methyl. We shall be concerned here only with the alkylated acids related to α- or 2-furoic acid. The β- or 3-furoic acids are dealt with later (p. 560).

5-Methyl-2-furoic acid has most frequently been synthesized by oxidation

[336] Gilman and Lichtenwalter, *Rec. trav. chim.*, **55**, 588 (1936).
[337] Monoya, *J. Pharm. Soc. Japan*, **447**, 357 (1919); *C. A.*, **13**, 2516 (1919).

of the corresponding aldehyde, 5-methylfurfural.[339, 350, 29, 223, 140, 340, 351, 352, 325, 327, 314, 116, 343] It has also been prepared from 2-methylfuran by metalation and subsequent carbonation,[344] and from 5-formyl-2-furoic acid by Wolff-Kizhner reduction of the aldehyde group.[345]



Yet another mode of preparation is that involving hydrolysis of the nitrile, and in this connection, attention is called to the anomalous behavior of furfuryl chloride when treated with aqueous alkali cyanide. Instead of the expected 2-furylacetonitrile (furfuryl cyanide) as reported by Kirner and Richter,[353] this reaction gives, as the major product, the isomeric 5-methyl-2-furonitrile. This important fact is clearly demonstrated by the work of Reichstein[m, 326] and of Johnson and his students.[325, 327] While the product distribution would be expected to vary depending upon the experimental conditions (choice of medium, particular metallic salt employed, concentration of cyanide ion, etc.), it was estimated that the nitrile obtained by Kirner and Richter was a mixture of the approximate composition shown below. For purposes of comparison the physical constants of the pure compounds are given in the diagram.

[m] Reichstein[354] has also shown that sorbyl chloride, $CH_3CH{=}CH{-}CH{=}CHCH_2Cl$, undergoes a similar rearrangement when treated with potassium cyanide.

[338] Hill, *Ber.*, **22**, 607 (1889).
[339] Bieler and Tollens, *Ann.*, **258**, 110 (1890).
[340] Masson, *Compt. rend.*, **149**, 795 (1909).
[341] Blanksma, *Chem. Weekblad*, **9**, 186 (1912); *C. A.*, **6**, 1433 (1912).
[342] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 249 (1932).
[343] Kühn, Köhler and Köhler, *Z. physiol. Chem.*, **247**, 197 (1937); *C. A.*, **31**, 6264 (1937).
[344] Gilman and Bebb, *J. Am. Chem. Soc.*, **61**, 109 (1939).
[345] Votoček and Krošlák, *Collection Czechoslov. Chem. Commun.*, **11**, 47 (1939); *C. A.*, **33**, 4983 (1939).
[346] Asahina and Yanagita, *Ber.*, **69**, 1646 (1936).
[347] Gilman, Calloway and Burtner, *J. Am. Chem. Soc.*, **57**, 906 (1935).
[348] Gilman, Burtner, Calloway and Turck, *J. Am. Chem. Soc.*, **57**, 907 (1935).
[349] Reichstein, Zschokke and Syz, *Helv. Chim. Acta*, **15**, 1112 (1932).
[350] Maquenne, *Ann. chim. phys.* (*6*), **22**, 76 (1891).
[351] Rinkes, *Rec. trav. chim.*, **49**, 1118 (1930).
[352] Rinkes, *Rec. trav. chim.*, **50**, 981 (1931).
[353] Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).
[354] Reichstein and Trivelli, *Helv. Chim. Acta*, **15**, 254 (1932).

TABLE 13. ALKYL-2-FUROIC ACIDS AND THEIR DERIVATIVES

Alkyl group	Acid, m.p., °C.	Derivatives, °C.			Ref.
		Esters	Acid chloride	Amide	
5-Methyl-	107–108, 109–110	ethyl, b.p. 88–89 (10 mm.)	m.p. 28 b.p. 82 (11 mm.), 202	m.p. 132	338, 339, 29, 223, 140, 340, 341, 326, 325, 327, 342, 314, 116, 343, 344, 345
4-Methyl-	128, 131–132	—	—	—	333, 332
3-Methyl- (Elsholtzia acid)	133–134, 136–137	methyl, m.p. 36–38 ethyl, m.p. 47–48, 49 b.p. 205	m.p. 18.5–19.5, 21–22 b.p. 80 (12 mm.), 192	85–86, 90–90.5 anilide, m.p. 91	89, 330, 346, 331
5-Ethyl-	94–95	—	—	—	329
5-*i*-Propyl-	65–66, 66–67	methyl, b.p. 110–112 (20 mm.) d_{25}^{25} 1.076; n_D^{25} 1.4851	b.p. 117–121 (16 mm.)	—	203, 109, 112
4-*i*-Propyl	—	—	—	—	347

5-*t*-Butyl-	104–105	methyl, b.p. 110–114 (15 mm.) d_{25}^{25} 1.037; n_D^{25} 1.4792 ethyl, b.p. 116–117 (16 mm.) trichloroethyl, b.p. 151–156 (16 mm.) d^{20} 1.261; n_D^{20} 1.5016 tribromoethyl, m.p. 62 trichloro-*i*-propyl, b.p. 162–164 (15 mm.) d^{20} 1.242; n_D^{20} 1.5006	b.p. 220 d_{25}^{25} 1.108; n_D^{25} 1.5091	m.p. 121 chloralamide, m.p. 139	109, 112, 110, 161
4-*t*-Butyl-	89	—	—	—	348
5-*t*-Pentyl	69–79	methyl, b.p. 108–110 (11 mm.) d_{25}^{25} 1.032; n_D^{25} 1.4804	—	α-naphthalide, m.p. 201	109, 112, 114
5-Hexyl-	36–37	methyl, b.p. 132–136 (19 mm.) d_{25}^{25} 1.016; n_D^{25} 1.4814	—	—	109
3,4-Dimethyl-	156–158	—	—	—	334
3,5-Dimethyl-	146–147	—	—	—	330
4,5-Dimethyl-	158.5–159	—	—	—	334
3,4,5-Trimethyl-	185 (dec.)	—	—	—	349

$C_4H_3O—CH_2Cl$

aq. NaCN

85 parts → $2,5\text{-}C_4H_2O—(CH_3)(CN)$

b.p. 74–75°C. (27 mm.)
d_4^{20} 1.0399, d_4^{25} 1.0348
n_D^{20} 1.4848

KOH

$2,5\text{-}C_4H_2O—(CH_3)(COOH)$

m.p. 109°C.

15 parts → $C_4H_3O—CH_2CN$[n]

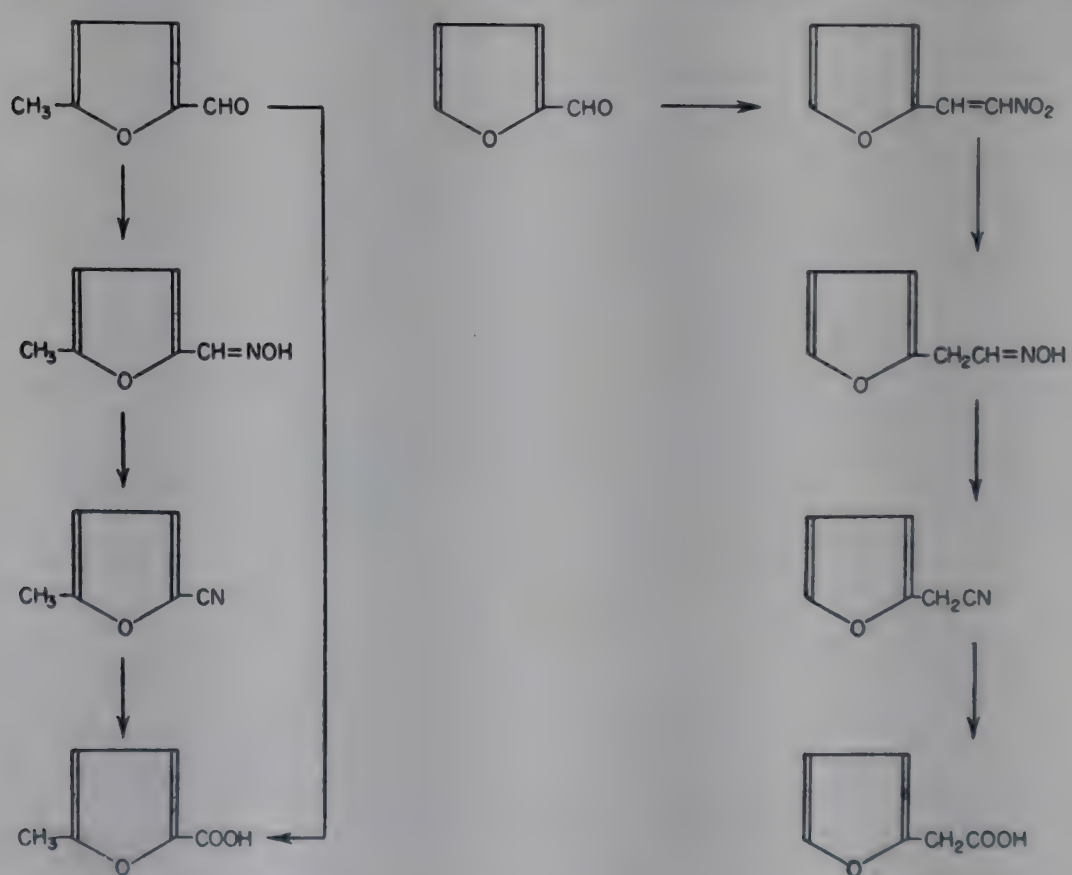
b.p. 78–80°C. (20 mm.)
d_4^{25} 1.0854
n_D^{25} 1.4715

KOH

$C_4H_3O—CH_2COOH$

m.p. 67–68°C.

The identity of the isomeric nitriles and carboxylic acids was established by independent and unequivocal synthesis as illustrated in the following diagram. In considering a mechanism which would account for the forma-



tion of 5-methyl-2-furonitrile from furfuryl chloride,[o] Scott and Johnson[327]

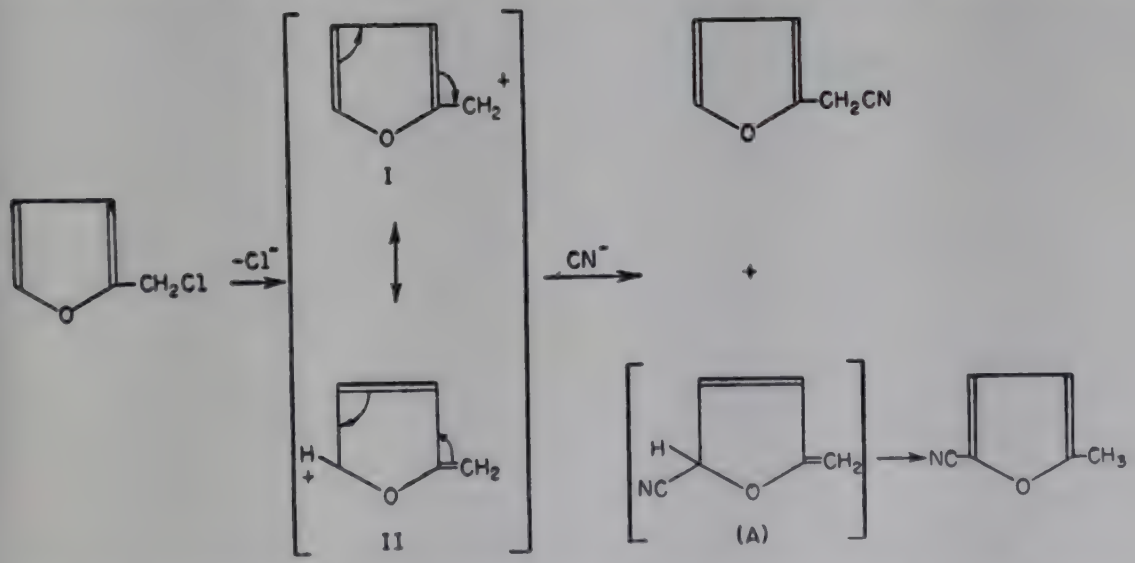
[n] Plucker and Amstutz[355] report the following constants for 2-furylacetonitrile b.p. 84° (17 mm.) n_D^{25} 1.4691.

[o] This reaction is related to the formation of levulinic acid from furfuryl alcohol (see Chapter 14), except that in the latter instance it is necessary to employ acidic conditions.

[355] Plucker and Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).

showed the inadequacy of an explanation based on rearrangement of the latter compound to 5-methyl-2-chlorofuran. They further demonstrated that no rearrangement takes place during the step of hydrolysis of the nitrile to the carboxylic acid. Thus, the critical reaction is that of formation of the nitrile, the reaction of furfuryl chloride with aqueous sodium cyanide. Reichstein[326] had postulated the formation of an unstable intermediate compound, 5-methylene-2,5-dihydro-2-furonitrile (A), which by rearrangement yielded 5-methyl-2-furonitrile. To account for the formation of (A), Scott and Johnson[327] proposed an initial step of reaction involving 1,4-addition of hydrogen cyanide to the furan nucleus, and subsequent loss of hydrogen chloride from the dihydrofuran derivative so formed.

Actually, the over-all reaction can be considered as a type of allylic rearrangement. That is, furfuryl chloride may be looked upon as a special type of allyl halide possessing a simple allylic structure and, in addition, an extended allylic system. In terms of modern concepts of displacement reactions, the mechanism can be formulated as a nucleophilic displacement on carbon; as proceeding by way of a cation resonating between the two structures I and II. This postulated cation could react with the available cyanide ions to give a mixture of 2-furylacetonitrile, and the intermediate compound (A).[p] The hydrogen atom attached to the number 5 nuclear carbon atom of (A) would be expected to be quite labile, inasmuch as it



occupies a position which is alpha to a nitrile group. This should facilitate prototropic rearrangement of (A) to the more stable 5-methyl-2-furonitrile structure.

[p] It is not possible, from existing information, to make a choice between two alternatives, (1) that the new C—CN bond is formed simultaneously with rupture of the old C—Cl bond (a push-and-pull type mechanism), or (2) that the carbonium ion (I ⟷ II) is actually set free as a transient intermediate. Possibly both mechanisms are operative. Unfortunately, the kinetics of the reaction have not been studied to date.

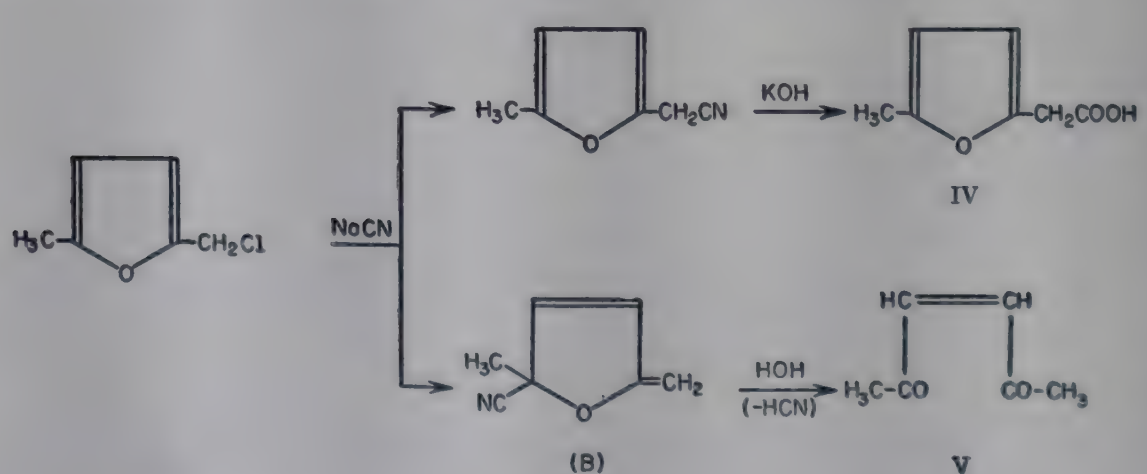
This abnormal reaction is probably common to all furfuryl halides[q] of the type $C_4H_3O—CRR'X$ (where R and R′ = H, alkyl or aryl) although further experimental work is required to establish the limitations. Reichstein and Zschokke[329] showed that this was true if R = H and R′ = CH_3. On hydrolysis of the nitrile formed by the action of aqueous potassium cyanide on the chloride or bromide derived from methylfurylcarbinol, these workers obtained 5-ethyl-2-furoic acid, III. It is likely that 5-*i*-propyl-2-furoic acid was formed in like manner when the tertiary halide obtained from dimethylfurylcarbinol was used as the starting material.[203]

$$C_4H_3O—\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CHCl}} \xrightarrow{KCN} 2,5\text{-}C_4H_2O—(CN)(CH_2CH_3) \xrightarrow{KOH}$$

$$2,5\text{-}C_4H_2O—(COOH)(CH_2CH_3)$$

III

On the other hand, similar treatment of 5-methylfurfuryl chloride produced 5-methyl-2-furylacetic acid,[r] IV, as the sole isolable product. It was concluded that the abnormal reaction requires the presence of a hydrogen atom in the 5-position of the furan ring.[342, 327] The validity of this hypothesis remains to be established. For example, the yield of IV is quite low, and the possibility may not be excluded that the loss is due to formation of (B). Unlike the abnormal intermediate from furfuryl chloride (see (A), above), (B) cannot undergo prototropic rearrangement. If formed, however, (B) might be expected to hydrolyze to the unsaturated diketone, V, which would be difficult to isolate, especially in alkaline medium.

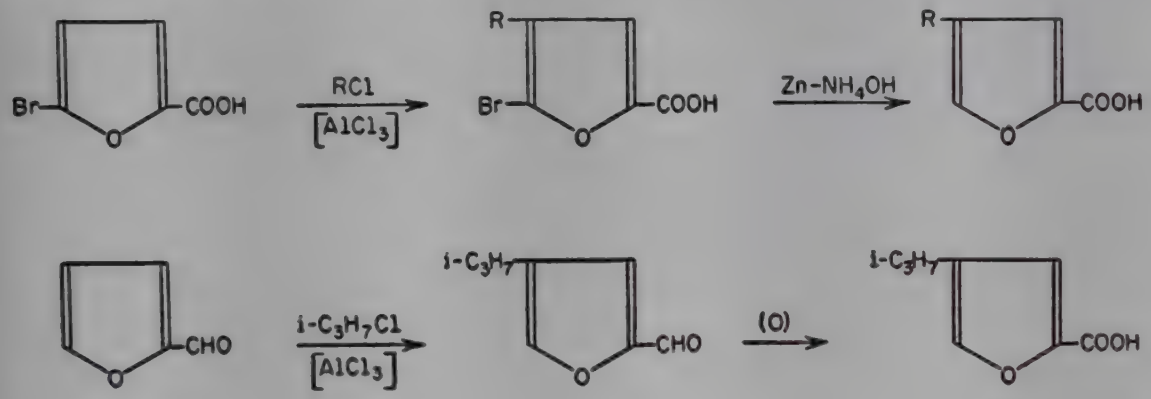


The 5-substituted homologs of 2-furoic acid (alkyl substituent = C_3—C_6, incl.) are readily obtained by Friedel-Crafts alkylation of 2-furoic ester

[q] 3-Furylmethyl chloride exhibits a similar behavior, but appears to give less of the abnormal product (Chapter 7).

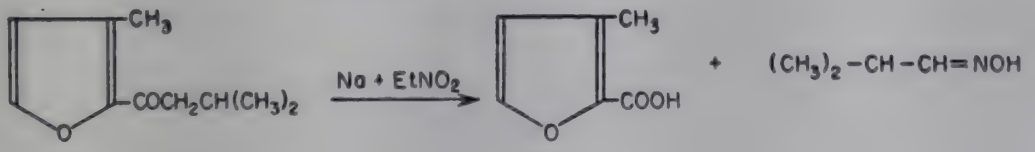
[r] It had been anticipated that some 2,5-dimethyl-3-furoic acid might be formed in this reaction, as a result of a rearrangement involving the nuclear hydrogen atom in the 3-position. The indications are that this did not occur [327]

and subsequent hydrolysis.[109, 110, 114] Regardless of the nature of the alkyl halide employed, this procedure invariably results in the introduction of a highly branched alkyl substituent (p. 499). Furthermore, it is limited to α-substitution of the furan nucleus and is, therefore, not applicable to the preparation of β-alkyl-2-furoic acids. On the other hand, by blocking the 5-position of 2-furoic ester with an easily removable substituent such as bromine, one may introduce an alkyl radical at the 4-position, and thereby obtain 4-alkyl-2-furoic acid by means of a subsequent operation.[112] In the special case of 4-*i*-propyl-2-furoic acid, VI, synthesis is readily accomplished from furfural, since on alkylation with *i*-propyl chloride, the incoming *i*-propyl residue is oriented abnormally to the 4-position.[347]



VI

The sole 3-substituted simple homolog which is known is 3-methyl-2-furoic acid, also known as Elsholtzia acid. From the essential oils of *Elsholtzia cristata*. Asahina and his co-workers[89] (see also [352]) isolated a ketone, VII (Elsholtzia ketone or Elsholtzione, see p. 430), which was converted by the action of sodium and ethyl nitrite to *i*-butyraldoxime and an acid, subsequently proven to be 3-methyl-2-furoic acid, VIII. Later VIII was prepared by oxidation of 3-methylfurfural with silver oxide,[330] and in low yield, along with 3-furylacetic acid, by hydrolysis of the mixed nitriles of these acids obtained by the action of aqueous potassium cyanide on 3-furylmethyl chloride[331] (see also Chapter 7).



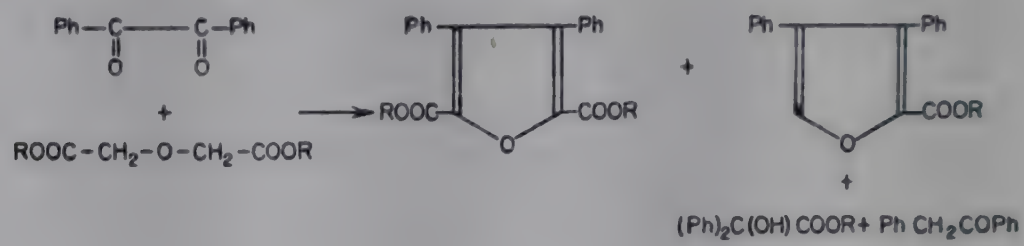
VII VIII

The di- and trimethyl-2-furoic acids listed in Table 13 were prepared from the corresponding aldehydes by oxidation.

Miscellaneous 2-Furoic Acids.

5-(1-Methylcyclohexyl)-2-furoic acid: m.p. 110°; from the methyl ester (b.p. 145–146° (11 mm.)) obtained by condensation of methyl 2-furoate with 1-methylcyclohexyl chloride in the presence of aluminum chloride.[114]

5-Benzyl-2-furoic acid: m.p. 167–169°; by oxidation of 5-benzylfurfural.[356]
3,4-Diphenyl-2-furoic acid: m.p. 234°; obtained along with its methyl ester (m.p. 124.5–126°) among the products formed by the condensation of benzil with diglycollic methyl ester[357] (see also [358]).



5-Hydroxymethyl-2-furoic Acids and Related Products

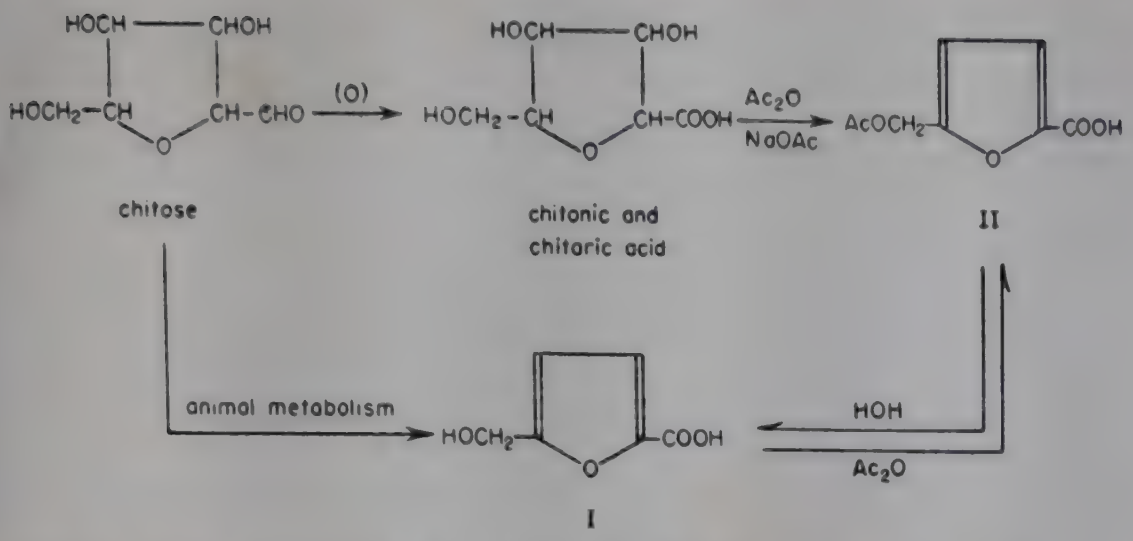
Hydroxyalkyl-2-furoic acids are unknown with the exception of the hydroxymethyl homolog with the substituent located in the 5-position. This acid and its derivatives, and the related ether, 5-(oxydimethylene)di-2-furoic acid, are the subject matter of this section.

5-Hydroxymethyl-2-furoic acid, I, was first described by Hill and Jennings[359, 29] who prepared it by the action of bromine on methylfuroic acid, followed by hydrolysis of the resulting bromomethyl derivative.[s] More commonly, however, the product has been derived from (hydroxymethyl)-furfural.[360, 361, 362, 363, 364, 365]

Fischer[366] obtained the hydroxy acid, as a by-product, in attempting to isomerize galactonic acid to talonic acid, and later[367] (see also [368]) synthesized it, in the form of the acetoxymethyl derivative, II, by heating chitonic or chitaric acids with acetic anhydride and sodium acetate. This synthesis starts with glucosamine which is converted into the anhydro sugar, chitose, by the action of nitrous acid. Oxidation of chitose produces the stereoisomeric chitonic and chitaric acids.

[s] This general procedure becomes more attractive in the light of the recent availability of (chloromethyl)furoic ester by direct chloromethylation of furoic ester (see later this section, and also p. 506).

[356] Fenton and Robinson, *J. Chem. Soc.*, **95**, 1334 (1909).
[357] Backer and Stevens, *Rec. trav. chim.*, **59**, 423 (1940).
[358] Hinsberg, *Ber.*, **45**, 2413 (1912).
[359] Hill and Jennings, *Proc. Am. Acad. Arts Sci.*, **27**, 186 (1892).
[360] Fenton and Gostling, *J. Chem. Soc.*, **75**, 423 (1899).
[361] Blanksma, *Chem. Weekblad*, **6**, 1047 (1909); *C. A.*, **5**, 1095 (1911).
[362] Blanksma, *Rec. trav. chim.*, **29**, 403 (1910).
[363] Angelico and Coppola, *Gazz. chim. ital.*, **42, II**, 583 (1912).
[364] Middendorp, *Rec. trav. chim.*, **38**, 1 (1919).
[365] Reichstein, *Helv. Chim. Acta*, **9**, 1066 (1926).
[366] Fischer, *Ber.*, **27**, 1524 (1894).
[367] Fischer and Andreae, *Ber.*, **36**, 2587 (1903).
[368] Haworth, Hirst and Nicholson, *J. Chem. Soc.*, **1927**, 1513.



Feeding tests conducted by Karashima[369, 370] (see also [371]) indicate that chitose is eliminated from the body of the rabbit, dog, chicken and frog in the form of (hydroxymethyl)furoic acid, although the latter was recovered in low yield (6.3 per cent max.). On the other hand, when chitonic acid was injected subcutaneously, none of the hydroxy acid could be found in the excrement. (Hydroxymethyl)- and (acetoxymethyl)furfural were both recovered as the hydroxy acid in good yield. In this connection, Sendju[372] (see also [373]) observes that in the dog, hunger or a fat and protein diet reduces the oxidation of (hydroxymethyl)furfural to I. Sumiki[374] (see also [375, 376]) reports I among the products of fermentation of glucose and sucrose by *aspergillus glaucus*.

5-Hydroxymethyl-2-furoic acid: (5-carboxyfurfuryl alcohol):

$$2,5\text{-}C_4H_2O\text{—}(COOH)(CH_2OH)$$

a colorless crystalline compound, the melting point of which has been variously reported between 162–163° to 166–167° (note: the product obtained by Kiermayer,[377] m.p. 148°, was apparently quite impure). It is soluble in water, alcohol and glacial acetic acid, very slightly so in ether, and insoluble in benzene, chloroform and carbon disulfide. **Ethyl ester,** m.p. 46°; b.p. 120–130° (0.02 mm.). Treatment of the ester with the appropriate halogen acid in dry ether produced the chloromethyl- and bromomethyl-furoic esters, the latter in 90 per cent yield[378]; **acid chloride,** b.p. 120° (9 mm.); with glycine, gives N-(5-hydroxymethyl-2-furoyl)glycine, m.p. 182°[369]; **amide,**

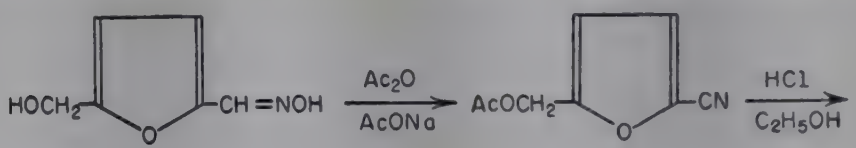
[369] Karashima, *Z. physiol. Chem.*, **169,** 278 (1927); *C. A.*, **21,** 3912 (1927).
[370] Karashima, *Z. physiol. Chem.*, **180,** 241 (1929); *C. A.*, **23,** 2175 (1929).
[371] Suzuki, *J. Biol. Chem.*, **38,** 1 (1919).
[372] Sendju, *J. Biochem. Japan*, **25,** 487 (1937); *C. A.*, **31,** 8562 (1937).
[373] Kageura, Sendzyu, Muraoka, Matuoka and Turu, *Japan J. Med. Sci. VIII Internal Med., Pediat. Psychiat.*, **5,** *Proc.* 59–60 (1938); *C. A.*, **35,** 169 (1941).
[374] Sumiki, *Bull. Agr. Chem. Soc. Japan*, **5,** 10 (1929); *C. A.*, **24,** 3813 (1930).
[375] Sumiki, *J. Agr. Chem. Soc. Japan*, **6,** 1153 (1930); *C. A.*, **25,** 2457 (1931).
[376] Sumiki, *J. Agr. Chem. Soc. Japan*, **7,** 819 (1931); *C. A.*, **26,** 1008 (1932).
[377] Kiermayer, *Chem. Ztg.*, **19,** 1003 (1895); *Chem. Centr.*, **1895, I,** 214.

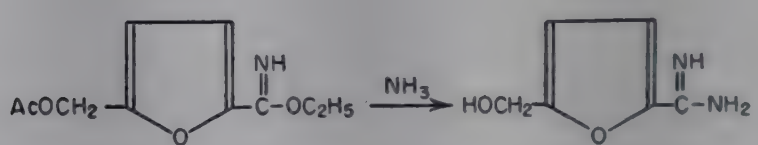
m.p. 151–152°[378]; **amidine** (hydrochloride, m.p. 147–148°; picrate, m.p. 223–225°), derived from 5-acetoxymethyl-2-furonitrile (see below) shows no activity against trypanosomes.[379]

5-Methoxymethyl-2-furoic acid: 2,5-C_4H_2O—(CH_2OCH_3)(COOH); m.p. 66.5°,[380] 67.5–68.5°,[380, 381] 72–73°.[368] **Methyl ester,** b.p. 61° (0.05 mm.); $n_D^{12.5}$ 1.4938.[368]

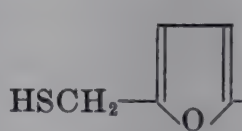
5-Ethoxymethyl-2-furoic acid: 2,5-C_4H_2O—($CH_2OC_2H_5$)(COOH); m.p. 57.5–58.5°,[380] 62°.[382, 364]

5-Acetoxymethyl-2-furoic acid: 2,5-C_4H_2O—(CH_2OAc)(COOH); m.p. 115–118°.[367, 362, 374, 368] The corresponding nitrile, **5-acetoxymethyl-2-furonitrile,** (b.p. 140° (0.01 mm.); n_D^{16} 1.4970) was obtained by refluxing 5-(hydroxymethyl)furfural oxime with acetic anhydride and fused sodium acetate.[379] The nitrile was converted into the ethyl imido-ester (hydrochloride, m.p. 121–121.5°), which on treatment with alcoholic ammonia produced 5-hydroxymethyl-2-furamide (5-amidinofurfuryl alcohol) [see constants above, under derivatives of (hydroxymethyl)furoic acid].





5-Mercaptomethyl-2-furoic acid:



m.p. 91–92°.[383]

The known halomethylfuroic acids and their derivatives are tabulated below. As expected, the halogen in these compounds is very reactive, and is replaceable by hydroxyl, cyanide, etc. Ethyl 5-bromomethyl-2-furoate on treatment with aqueous ammonia was readily transformed into the tertiary amine, tris(5-carbethoxyfurfuryl)amine, m.p. 76°.[378]

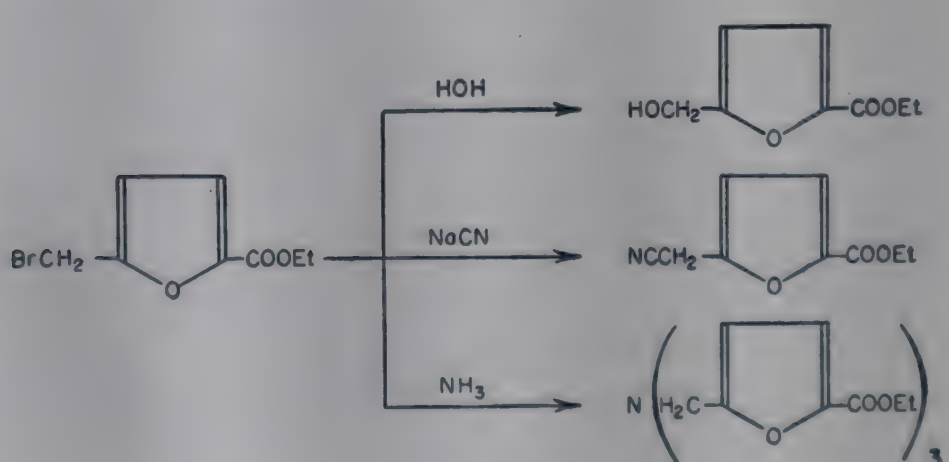


TABLE 14. 5-HALOMETHYL-2-FUROIC ACIDS AND DERIVATIVES

Substituent in 5-position	M.p. (°C.)	Derivatives (°C.)	Ref.
Chloromethyl	—	methyl ester, b.p. 136 (15 mm.) ethyl ester, b.p. 150–152 (25 mm.), 115 (0.015 mm.) n_D^{20} 1.5103 *n*-butyl ester, b.p. 134–135 (5 mm.)	130, 131, 378
Bromomethyl	147–148	ethyl ester, b.p. 125 (0.005 mm.) n_D^{18} 1.5414	29, 378; see also 360
Dibromomethyl	153	acid bromide, m.p. 102	223

5-Aminomethyl-2-furoic acid: 2,5-C_4H_2O—$(CH_2NH_2)(COOH)$; reported as the hydrochloride, m.p. 245° (chloroplatinate, m.p. 202°) by hydrolysis of 5-chloroacetamidomethyl-2-furoic acid with aqueous hydrochloric acid.[132] Attempts to derive it similarly (or by alkaline fission) from the benzamidomethyl- derivative, resulted in resin formation.[133] The following 5-acylaminomethyl-2-furoic acids and esters were prepared by condensation of furoic acid or ester with the appropriate N-(hydroxymethyl)amide in concentrated sulfuric acid (see p. 508).

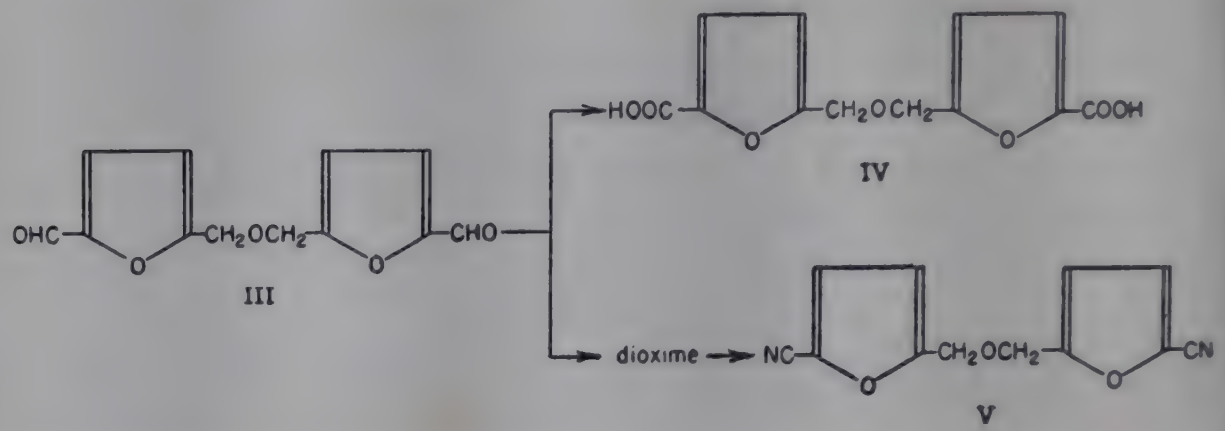
5-chloroacetamidomethyl-	m.p. 90°[132]
*5-benzamidomethyl-	m.p. 189–191°; ethyl ester, m.p. 125–127°[133]
5-*p*-toluamidomethyl-	m.p. 195–197°[133]
5-*o*-nitrobenzamidomethyl-	m.p. 195–198°[133]
5-phthalamidomethyl-	m.p. 204°[132]
5-phthalimidomethyl-	ethyl ester, m.p. 118°[132]

* Apparently exists in stable and unstable forms.[133] Decarboxylation of these acids produces the corresponding acylated furfurylamine.[133]

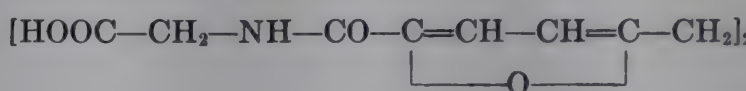
When 5-(hydroxymethyl)furfural is distilled, it is partially converted to the ether, 5-(oxydimethylene)di-2-furfural, III, from which the corresponding dicarboxylic acid, IV, has been derived by animal metabolism,[384, 385] and by oxidation with silver oxide.[385] The dinitrile, V, has likewise been synthesized from III, by way of the oxime which was dehydrated over

[378] Haworth and Jones, *J. Chem. Soc.*, **1944**, 667.
[379] Newth and Wiggins, *J. Chem. Soc.*, **1947**, 396.
[380] Cooper and Nuttall, *J. Chem. Soc.*, **99**, 1193 (1911).
[381] Wolfrom, Wallace and Metcalf, *J. Am. Chem. Soc.*, **64**, 265 (1942).
[382] Fischer and Neyman, *Ber.*, **47**, 973 (1914).
[383] Kipnis, Levy and Ornfelt, *J. Am. Chem. Soc.*, **71**, 2270 (1949).
[384] Iseki, *Z. physiol. Chem.*, **216**, 130 (1933); *C. A.*, **27**, 2953 (1933)
[385] Iseki and Sugiura, *J. Biochem Japan*, **30**, 113 (1939); *C A.*, **34**, 2370 (1940).

acetic anhydride.[379] These binuclear products are included in this section because of their relationship to (hydroxymethyl)furoic acid.



5-(Oxydimethylene)di-2-furoic acid: [ether of 5-hydroxymethyl-2-furoic acid]; II, above; m.p. 209–210°. **Dichloride** (by action of $SOCl_2$), m.p. 98–99°. **Esters:** Monomethyl, m.p. 144–146°; dimethyl, m.p. 154°; diethyl, m.p. 71°; bis-2-chloroethyl, m.p. 78–79°.[385] **Diamide,** m.p. 204°; **dianilide,** m.p. 169°; ***o*-hydroxyanilide,** m.p. 329°. **5-(Oxydimethylene)di-N-2-furoylglycine,**



m.p. 223°; diethyl ester, m.p. 107°; from the dichloride and aminoacetic ester.[386] The **dinitrile,** m.p. 57–58°, was converted to the bisethyl imidoester (hydrochloride, m.p. 134–135° (dec.)), from which was obtained the diamidine (5,5′-diamidinofurfuryl ether), m.p. 198–198.5°. The latter has no action on trypanosomes.[379]

Acylfuran-2-carboxylic Acids

Included here are those few 2-furoic acids and esters which possess one or more nuclear substituents containing aldehyde or ketone groups. The latter types have been, for the most part, prepared by acylation of the appropriate ester by means of the Friedel-Crafts technique, which reaction is discussed elsewhere (p. 501).

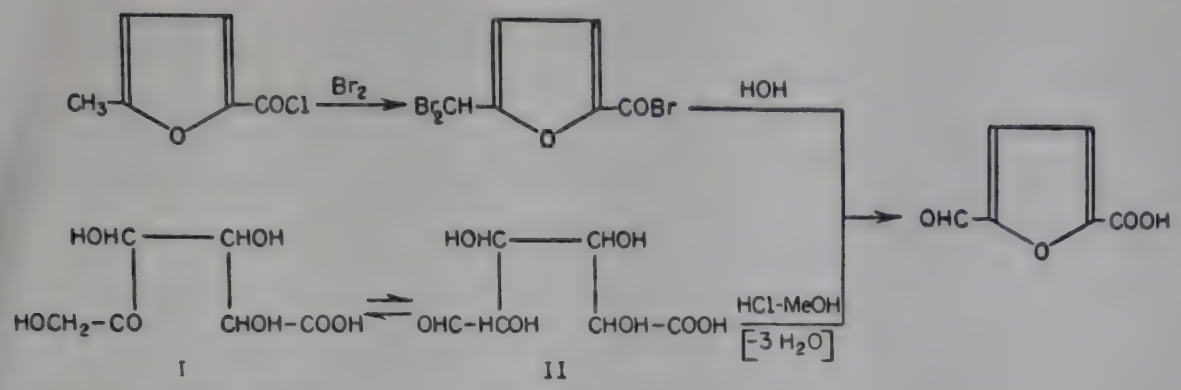
5-Formyl-2-furoic acid: [5-carboxyfurfural]; 2,5-C_4H_2O—(COOH)(CHO); m.p. 201–202°, 206–207°. Obtained (1) by the action of bromine on 5-methyl-2-furoic acid, or preferably the acid chloride, in direct sunlight with formation of 5-dibromomethyl-2-furoyl bromide (m.p. 102°) and subsequent hydrolysis[223]; (2) by heating 5-ketogluconic acid (I) with methanolic hydrogen chloride, a reaction apparently involving isomerization to the aldogluconic acid (II) and dehydration with ring closure to the aldo-furoic acid.[387, 388, 345]

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[386] Iseki and Sugiura, *J. Biochem Japan*, **30**, 119 (1939); *C. A.*, **34**, 2366 (1940).

[387] Votoček and Malachta, *Collection Czechoslov. Chem. Commun.*, **6**, 241 (1934); *C. A.*, **29**, 469 (1935).

[388] Votoček and Krošlák, *Collection Czechoslov. Chem. Commun.*, **10**, 259 (1938); *C. A.*, **32**, 8410 (1938).



Oxime, m.p. 224–226° (dec.); **phenylhydrazone,** m.p. 176° (dec.).

Methyl ester, phenylhydrazone, m.p. 183°; **methyl ester,** cyanohydrin, m.p. 91.5°. The compound behaves normally as an aldehyde; Wolff-Kizhner reduction produces methylfuroic acid; condensation with malonic acid, in the presence of pyridine at 100°, proceeds with loss of carbon dioxide and formation of carboxyfurylacrylic acid; with diazomethane, acetylfuroic acid is obtained; it undergoes the Cannizzaro reaction on boiling with barium hydroxide; oxidation with silver oxide gives furan-2,5-dicarboxylic acid. Attempted benzoin-type condensation of the methyl ester produced instead the cyanohydrin, which on hydrolysis was converted into 5-carbomethoxy-2-furylglycollic acid.

3-Formyl-2-furoic acid: [2-carboxy-3-furaldehyde]; 2,3-C_4H_2O—(COOH)(CHO); m.p. 158°; **oxime,** m.p. 225°; **phenylhydrazone,** m.p. 171° (dec.). Product derived from 3-methyl-2-furoyl chloride (Elsholtzia acid chloride) by oxidation with bromine in direct sunlight and subsequent hydrolysis of the dibromomethyl intermediate product (see p. 130). Oxidation with silver oxide produced 2,3-furandicarboxylic acid. Dehydration of the oxime derivative on refluxing in acetic anhydride gave rise to the nitrile-acid, 3-cyano-2-furoic acid, m.p. 183°.[89]

5-Acetyl-2-furoic acid: 2,5-C_4H_2O—($COCH_3$)(COOH); **ethyl ester,** m.p. 85–86°, obtained in 30 per cent yield from ethyl 2-furoate (0.4 mole), acetic anhydride (0.4 mole) and stannic chloride (0.8 mole) in benzene. The keto acid, obtained by alkaline hydrolysis of the ester, did not melt up to 230°, but decomposed slowly with blackening. Decarboxylation of the keto acid in the presence of copper-bronze produced methyl 2-furyl ketone.[109] **Methyl ester,** m.p. 103°, obtained by the action of diazomethane on methyl 5-formyl-2-furoate.[345]

5-*n*-Butyryl-2-furoic acid: 2,5-C_4H_2O—(COC_3H_7)(COOH); m.p. 172°, by hydrolysis of the **methyl ester,** m.p. 67–68°, obtained in 25 per cent yield from methyl 2-furoate, *n*-butyric anhydride and stannic chloride in benzene. Decarboxylation gave *n*-propyl 2-furyl ketone.[109]

5-Methyl-4-acetyl-2-furoic acid: 2,4,5-C_4HO—(COOH)($COCH_3$)(CH_3); m.p. 235° (dec.), from the **ethyl ester,** m.p. 99°, obtained in 54 per cent yield from ethyl 5-methyl-2-furoate (0.17 mole), acetic anhydride (0.17 mole) and stannic chloride (0.34 mole) in benzene at 60° for 24 hours. Oxidation produced 5-methyl-2,4-furandicarboxylic acid.[116]

2-Carboxyfurylalkanoic and -alkenoic Acids

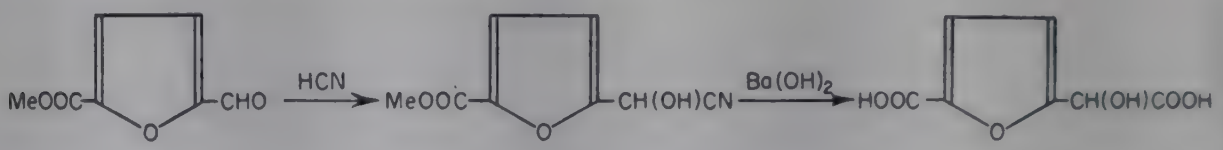
5-Carboxy-2-furylacetic acid: [5-carboxymethyl-2-furoic acid];

2,5-C_4H_2O—(COOH)(CH_2COOH)

m.p. 217°; by saponification of the ethyl 5-cyanomethyl-2-furoate (m.p. 42–43°; b.p.

120° (bath temp.) at 0.012 mm.) obtained by treatment of ethyl 5-bromomethyl-2-furoate with sodium cyanide.[378]

5-Carboxy-2-furylglycollic acid: II; does not melt up to 300°; by saponification of the cyanohydrin derived from methyl 5-formyl-2-furoate, I, and hydrogen cyanide.[388] The **half-ester,** 5-carbomethoxy-2-furylglycollic acid (m.p. 238–239°) was obtained by refluxing I with aqueous potassium cyanide.[345]



I II

3-(5-Carboxy-2-furyl)propionic acid: 2,5-C_4H_2O-(COOH)(CH_2CH_2COOH); m.p. 180°; by reduction of the corresponding derivative of acrylic acid (see below), using sodium amalgam.[345]

3-(5-Carboxy-2-furyl)acrylic acid: 2,5-C_4H_2O—(COOH)(CH=CHCOOH); m.p. 273–274°, 277°. Isolated from the urine of dogs which had been fed 3-(5-acetoxymethyl-2-furyl)acrylic acid,[389] and in the form of the carboxyfurylacrylamide, m.p. 280°, from rabbit urine on feeding 3-(5-methyl-2-furyl)acrylamide.[343]

Both the dicarboxylic acid and its **half-ester,** the 5-carbomethoxyfurylacrylic acid (m.p. 206–208°), were synthesized by condensing 5-formyl-2-furoic acid and its methyl ester with malonic acid in the presence of pyridine.[345]

3-Furancarboxylic Acids

3-Furoic Acid

One of the earliest known β-monosubstituted furan compounds was 3-furoic acid;[t] isolated from the residue left behind on steam distillation of an alcoholic extract of the root bark of *Evonymus atropurpureus* Jacquin, also known as "wahoo" or "burning bush".[145] Another natural source is the root of the scarlet runner bean (*phaseolus multiflorus*).[392] The acid has also been derived from *Perilla* ketone (3-isobutyrylfuran), the principal constituent of the essential oil of *Perilla frutescens*[393] (see also [394]), and by the action of potassium ferricyanide on ngaiona, from the leaves of *Myoporum laetum*.[395]

The structure assigned by Rogerson[145] was confirmed by the synthesis of 3-furoic acid from 2,4- and 2,3-furandicarboxylic acids by partial decarboxylation[81] (see also [80]). It has also been prepared in similar manner from the 3,4-dicarboxylic acid, the 2,3,4-tricarboxylic acid, and the tetracarboxylic acid.[82] The method of stripping carboxyl groups from the last

[t] The so-called "β-pyromucic acid" reported by Stenhouse,[390, 391] was actually impure 2-furoic acid, a mixture of the latter with 5-methyl-2-furoic acid.[339]

[389] Karashima, *Z. physiol. Chem.*, **184,** 265 (1929); *C. A.*, **24,** 362 (1930).

[390] Stenhouse, *Ann.*, **74,** 278 (1850).

[391] Stenhouse, *Ann.*, **163,** 185 (1872).

[392] Power and Salaway, *Pharm. J.* (4), **36,** 550 (1913); *Chem. Centr.*, **1913, I,** 1931.

[393] Sebe, *J. Chem. Soc. Japan*, **64,** 1130 (1943); *C. A.*, **41,** 3785 (1947).

[394] Goto, *J. Pharm. Soc. Japan*, **57,** 77 (1937); *C. A.*, **31,** 4056 (1937).

[395] Brandt and Ross, *J. Chem. Soc.*, **1949,** 2778.

named compound is reported to be the best available procedure for the synthesis of 3-furoic acid.[396, 397, 331]

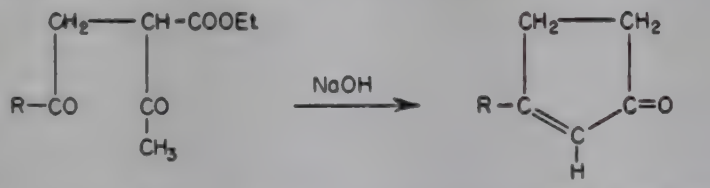
3-Furoic acid (m.p. 122–123°, corr.) is sparingly soluble in cold water, but readily soluble in hot water, alcohol and ethyl acetate. It is volatile with steam and sublimes readily on heating. The reactions of the carboxyl group proceed normally with formation of the appropriate derivatives. Nitration and bromination introduce the corresponding substituent into the alpha nuclear position farthest removed from the carboxyl group.[80] Reduction with lithium aluminum hydride produces 3-furylcarbinol in high yield.[331]

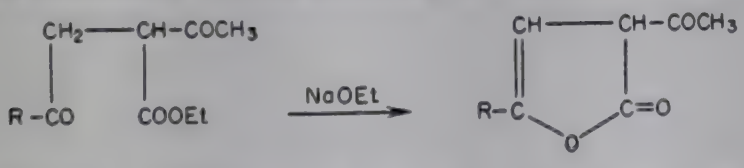
Derivatives of 3-furoic acid: Esters: methyl, b.p. 160°; d_{15}^{15} 1.744; n_D^{20} 1.46759[145]; b.p. 180–181°[394]; ethyl, b.p. 65–67° (14 mm.); d_{20}^{20} 1.038; n_D^{20} 1.4592[80]; b.p. 172°.[394] **3-Furoyl chloride,** m.p. 29°; b.p. 65° (47 mm.).[80] **Amide,** m.p. 168–169°; from the acid chloride and ammonia[80, 81] and also by rearrangement of 3-furaldoxime over Raney nickel.[398] **Anilide,** m.p. 131–132°[81]; m.p. 129.5°.[394] **Hydrazide,** m.p. 124–124.5°.[399] **Azide,** not isolated but decomposed to 3-furyl isocyanate, which with PhMgBr produced 3-benzamidofuran.[399]

Many substituted 3-furoic acids are obtainable by condensation of α-chloro aldehydes and ketones with β-keto esters. Paal[400] reacted chloroacetone with ethyl sodioacetoacetate and obtained ethyl acetonylacetoacetate, (A), from which he derived 2,5-dimethyl-3-furoic acid, I, (see [401]) on subsequent treatment with hydrochloric acid.[u] It is certain from this evidence that C-alkylation of the acetoacetic ester occurred in Paal's work.

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[u] Failure to find 2,5-dimethyl-3-furoic acid as a product in the work of Hantzsch[402] is explainable in terms of the experimental conditions. Ring closure of A, a 1,4-dicarbonyl compound, to a furan derivative requires acidic conditions. Under alkaline conditions, different condensations occur. Ammonia promotes cyclization to a pyrrole (see text). Cyclopentenones are formed in the presence of aqueous sodium hydroxide.[403, 404] Sodium ethoxide, however, promotes lactonization.[405, 404] Pyrolysis by distillation at atmospheric pressure yields not only this lactone, but also some 2,5-dimethyl-3-furoic ester.





[396] Gilman, Oatfield and Kirkpatrick, *Proc. Iowa Acad. Sci.*, **40**, 112 (1933); *C. A.*, **29**, 2532 (1935).

[397] Kirkpatrick, *Iowa State Coll. J. Sci.*, **11**, 75 (1936).

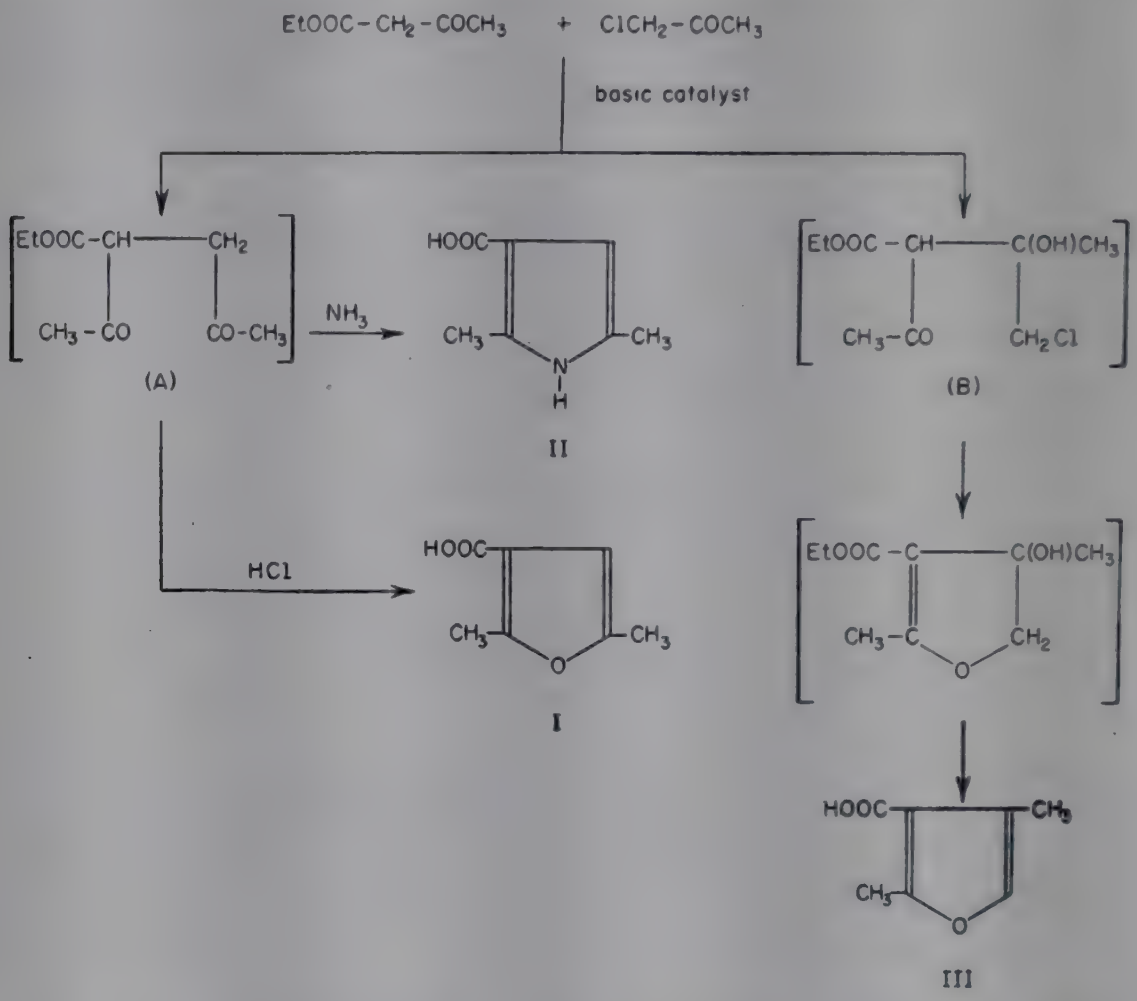
[398] Bryson and Dwyer, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 471 (1941).

[399] Burtner, *J. Am. Chem. Soc.*, **56**, 666 (1934).

[400] Paal, *Ber.*, **17**, 2756 (1884).

[401] Hurd and Wilkinson, *J. Am. Chem. Soc.*, **70**, 739 (1948).

C-alkylation likewise explains the direct[u] formation of 2,5-dimethyl-3-pyrrolecarboxylic acid, II, when chloroacetone and acetoacetic ester are condensed in an excess of aqueous ammonia,[402] but according to Feist,[406] there is also formed 2,4-dimethyl-3-furoic acid, III. Feist postulated an O-alkylation intermediate to account for the latter, but the existing evidence[407] is in favor of the aldol-like condensation product, B.[v]

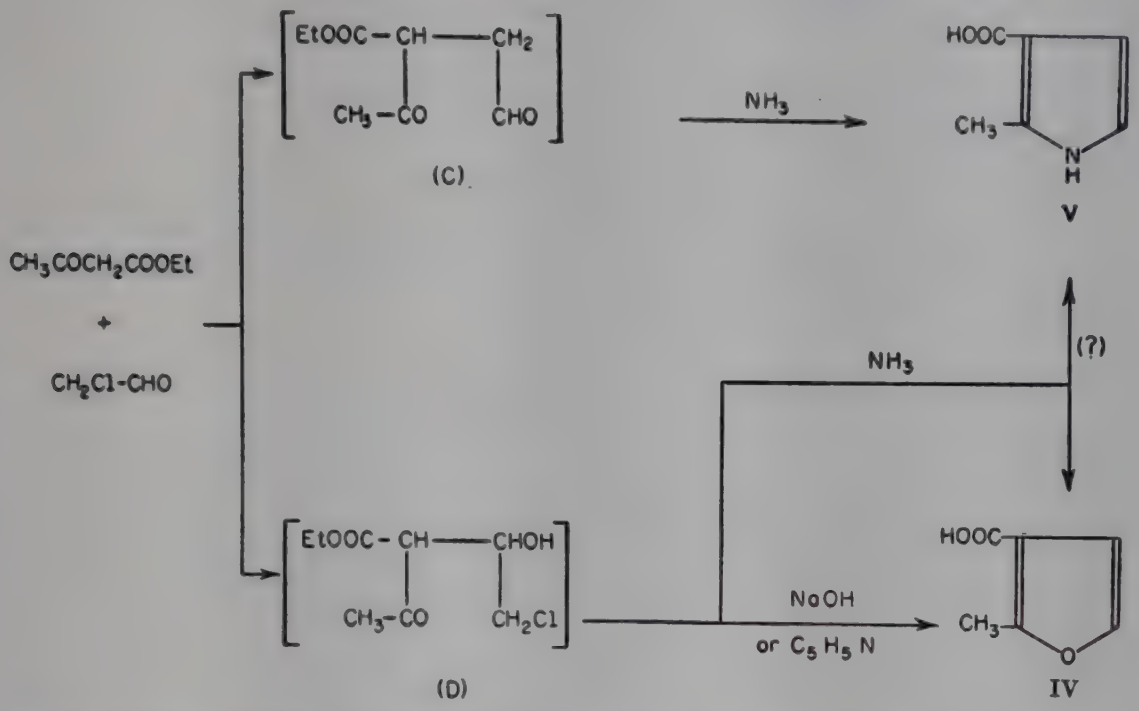


The Benary[409] modification of Feist's synthesis, involving reaction of 1,2-dichloroethyl ethyl ether with acetoacetic ester in aqueous ammonia, produces a mixture of 2-methyl-3-furoic acid, IV, and 2-methyl-3-pyrrolecarboxylic acid, V. In this reaction the haloether is converted into chloroacetaldehyde which then condenses with the keto ester. From the stand-

[v] Recently Alexander and Baldwin[408] have demonstrated that the so-called O-alkylated derivative of acetoacetic ester is actually a mixture of the ethyl ester and the amide of III.

[402] Hantzsch, *Ber.*, **23**, 1474 (1890).
[403] Borsche and Fels, (a) *Ber.*, **39**, 1809 (1906); (b) *Ibid.*, **39**, 1922 (1906).
[404] Wilds and Johnson, *J. Am. Chem. Soc.*, **67**, 286 (1945).
[405] Borsche and Spannagel, *Ann.*, **331**, 298 (1904).
[406] Feist, *Ber.*, **35**, 1545 (1902).
[407] Dunlop and Hurd, *J. Org. Chem.*, **15**, 1160 (1950).
[408] Alexander and Baldwin, *J. Am. Chem. Soc.*, **73**, 356 (1951).
[409] Benary, *Ber.*, **44**, 493 (1911).

point of the yield of the furan acid, it is advantageous to use sodium hydroxide[80, 410] or pyridine[327] instead of ammonia. If, as in the preceding synthesis, one assumes preliminary formation of two different intermediates, C and D, a possible explanation suggests itself. Under the influence of ammonia, the aldolization intermediate, D, might be expected to cyclize to either IV or V, whereas the other bases restrict ring closure of D to the furan acid, IV.

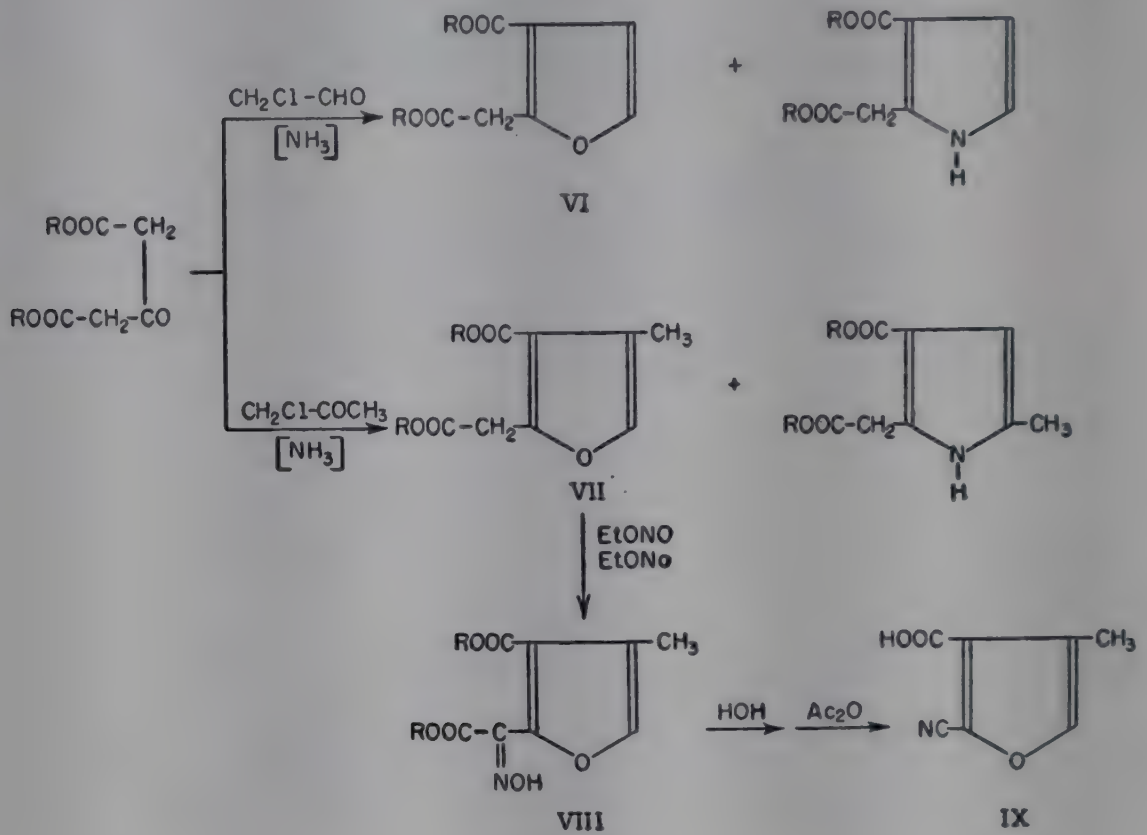


This general reaction has been applied to β-keto esters other than acetoacetic ester, giving rise to a variety of substituted 3-furoic acids. Thus, 2-*i*-propyl-,[203] 2-phenyl-,[411] 2-*p*-chlorophenyl-,[412, 413] 2-(2-pyridyl)-,[414] 2-(3-pyridyl)-,[415] and 2-(2-furyl)-3-furoic acids[411, 320] have been synthesized from the appropriate acylacetic esters by condensation with 1,2-dichloroethyl ethyl ether.

β-Ketoglutaric ester in the Benary and Feist syntheses produces the esters of 2-carboxymethyl-3-furoic acid, VI[416, 81] and 4-methyl-2-carboxymethyl-3-furoic acid, VII[417], respectively. The reactive methylene group of these esters permits the introduction of a nitroso group on treatment with ethyl nitrate and sodium ethoxide. Saponification of the resulting oximino ester, VIII, to the free dicarboxylic acid, and subsequent warming with acetic anhydride results in the loss of carbon dioxide and rearrangement to

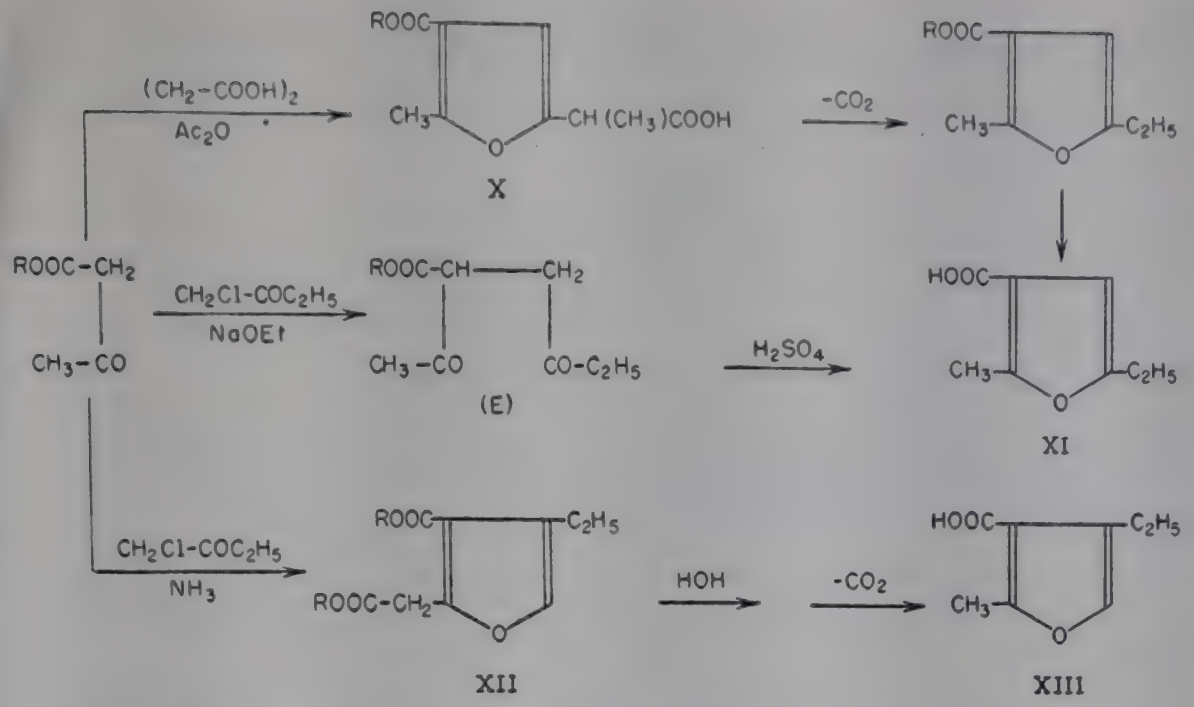
[410] Gilman, Burtner and Smith, *Rec. trav. chim.*, **51**, 407 (1932).
[411] Kondo and Suzuki, *J. Pharm. Soc. Japan*, **544**, 501 (1927); *C. A.*, **21**, 3362 (1927).
[412] Wibaut and Dhont, *Rec. trav. chim.*, **62**, 272 (1943).
[413] Johnson, *J. Chem. Soc.*, **1946**, 895.
[414] Wibaut, *Rec. trav. chim.*, **45**, 657 (1926).
[415] Lions and Ritchie, *J. Proc. Roy. Soc. N. S. Wales*, **74**, 110 (1940).
[416] Fujita, *J. Pharm. Soc. Japan*, **519**, 450 (1925); *C. A.*, **20**, 757 (1926).
[417] Feist and Molz, *Ber.*, **32**, 1766 (1899).

the appropriate nitrile, IX, from which the corresponding 2,3-furandicarboxylic acid may be obtained.[332, 81, 333] The reactions involved are illustrated below.

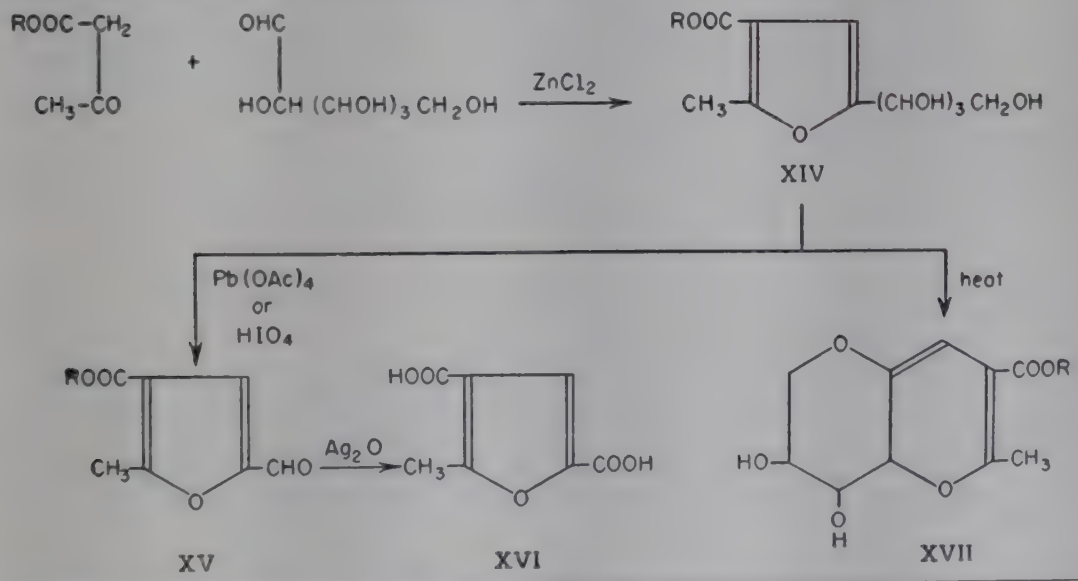


An isomer of VII, 5-carboxymethyl-2-methyl-3-furoic acid (the so-called methronic acid) is obtained by condensation of acetoacetic ester with either sodium succinate[418] (see also [419, 420, 421, 422]) or glyoxal.[423] When methylsuccinic acid is used instead of succinic acid, there is formed 5-(1-carboxyethyl)-2-methyl-3-furoic acid, X (R = H), which loses carbon dioxide on heating to give 5-ethyl-2-methyl-3-furoic acid, XI. Structures X and XI were clarified by the efforts of Reichstein[349, 424] who showed that XI may also be synthesized from sodioacetoacetic ester and chloromethyl ethyl ketone by ring closure of the intermediate α-acetyl-β-propionylpropionic ester, E. When the same ketone was reacted with ethyl acetoacetate in ammoniacal ether according to the Feist synthesis, XII was obtained in low yield, from which XIII was derived by partial decarboxylation.[424]

[418] Trefil'ev, *Ukrainski Khem. Zhur.*, **1**, *Sci. Pt.*, 121 (1925); *C. A.*, **23**, 3926 (1929).
[419] Fittig, *Ber.*, **18**, 2526 (1885).
[420] Fittig, *Ann.*, **250**, 166 (1889).
[421] Schroeter, *Ber.*, **39**, 2129 (1906).
[422] Feist and Hantzsch, *Ber.*, **21**, 3189 (1888).
[423] Polonowsky, *Ann.*, **246**, 1 (1888).
[424] Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 6 (1933).



Condensation of glucose or mannose with β-keto esters in the presence of zinc chloride also gives rise to derivatives of 3-furoic acid.[425, 426, 427, 428, 429, 430] Using acetoacetic ester, there is obtained 5-tetrahydroxybutyl-2-methyl-3-furoic ester, XIV, which on oxidation with lead tetraacetate or periodic acid is converted into 5-formyl-2-methyl-3-furoic ester, XV. The latter on further oxidation with silver oxide produces the corresponding furandicarboxylic acid, XVI. On heating at 170° or by refluxing in aqueous solution, XIV undergoes rearrangement with loss of water to form the hexahydro-4,8-dioxanaphthalene derivative, XVII.[430]



[425] Müller and Vargha, *Ber.*, **72**, 1993 (1939).

[426] Vargha, *Magyar Biol. Kutatointezet Munkai*, **12**, 359 (1940); *C. A.*, **35**, 1034 (1941).

[427] Szeki and Laszlo, *Ber.*, **73**, 924 (1940).

Nuclear Substituted 3-Furoic Acids

Alkyl- and Aryl-3-furoic Acids.

Monosubstituted

2-Methyl-3-furoic acid: 2,3-$C_4H_2O(CH_3)(COOH)$; m.p. 101–102°, 102–103°; by condensation of acetoacetic ester with 1,2-dichloroethyl ethyl ether in aqueous ammonia[409, 89] (see also [431]), in aqueous sodium hydroxide,[431a, 410] and in aqueous pyridine.[327, 314] Also obtained by partial decarboxylation of 2-methyl-3,5-furandicarboxylic acid.[116, 428] Derivatives: **ethyl ester,** b.p. 49.5° (10 mm.), 57° (17 mm.); d_4^{25} 1.0102[155]; **acid chloride,** b.p. 68–70.5° (14 mm.)[89]; **amide,** m.p. 90°[428]; **anilide,** m.p. 111–112°[428]; **hydrazide,** m.p. 148°, 149.5–150°, 152–153°[399, 314, 317]; **azide,** m.p. 22–23°; converted into 2-methyl-3-furyl isocyanate, b.p. 42° (15 mm.), which with PhMgBr produced 2-methyl-3-benzamidofuran, m.p. 137.8–138°.[399, 314]

4-Methyl-3-furoic acid: 3,4-$C_4H_2O(COOH)(CH_3)$; m.p. 138–139°, by partial decarboxylation of 4-methyl-2,3-furandicarboxylic acid.[332] **Acid chloride,** b.p. 59° (11 mm.).[334] Bromination, nitration and mercuration result in substitution in the 5-position.[432]

5-Methyl-3-furoic acid: 3,5-$C_4H_2O(COOH)(CH_3)$; m.p. 119°, by Wolff-Kizhner reduction of 5-formyl-3-furoic acid.[433]

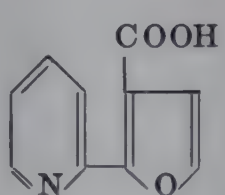
2-*i*-Propyl-3-furoic acid: 2,3-$C_4H_2O(i\text{-}C_3H_7)(COOH)$; m,p. 79°, by hydrolysis of the ethyl ester (b.p. *ca.* 92° (12 mm.)) obtained by condensation of *i*-butyrylacetic ester with 1,2-dichloroethyl ethyl ether in aqueous sodium hydroxide.[203, 434]

2-Phenyl-3-furoic acid: 2,3-$C_4H_2O(C_6H_5)(COOH)$. **Ethyl ester,** b.p. 148–154° (6 mm.), by condensation of benzoylacetic ester with 1,2-dichloroethyl ethyl ether according to Benary procedure[411] (see also [416]).

5-Phenyl-3-furoic acid: 3,5-$C_4H_2O(COOH)(C_6H_5)$; m.p. 208–209°. Derived from 2-phenyl-4-benzoylfuran by way of the oxime. Beckmann rearrangement produced **5-phenyl-3-furanilide,** m.p. 192–193°, which was hydrolyzed to the free acid.[435]

2-*p*-Chlorophenyl-3-furoic acid: 2,3-$C_4H_2O(C_6H_4Cl\text{-}p)(COOH)$; m.p. 193–194°, from the **ethyl ester,** (m.p. 63°; b.p. 132–135° (15 mm.)) formed by condensation of *p*-chlorobenzoylacetic ester with 1,2-dichloroethyl ethyl ether according to the Benary procedure.[412, 413]

2-(2-Pyridyl)-3-furoic acid:



reported as the **ethyl ester** (picrate, m.p. 204–205°; chloroaurate, m.p. 144–145°) as a

[428] Gonzalez, *Anales soc. espan. fis. quim.*, **32,** 815 (1934); *C. A.*, **29,** 1088 (1935).

[429] Gonzalez and Aparicio, *Anales fis. y quim. Madrid*, **41,** 846 (1945); *C. A.*, **41,** 6558 (1947).

[430] Jones, *J. Chem. Soc.*, **1945,** 116.

[431] Plancher and Albini, *Atti acad. Lincei* (*5*), **13, I,** 39 (1904); *Chem. Centr.*, **1904, I,** 955.

[431a] Gilman and Burtner, *Iowa State Coll. J. Sci.*, **5,** 189 (1931).

[432] Gilman and Burtner, *J. Am. Chem. Soc.*, **71,** 1213 (1949).

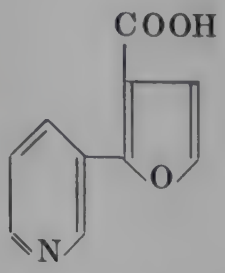
[433] Gilman, Burtner and Smith, *J. Am. Chem. Soc.*, **55,** 403 (1933).

[434] Reichstein and Hirt, *Helv. Chim. Acta*, **16,** 121 (1933).

[435] Fuson, Fleming and Johnson, *J. Am. Chem. Soc.*, **60,** 1994 (1938).

product of the condensation of picolinylacetic ester with chloroacetaldehyde in aqueous ammonia.[414]

2-(3-Pyridyl)-3-furoic acid:



m.p. 225°, by hydrolysis of the **ethyl ester** (b.p. 148° (1.5 mm.); picrate m.p. 153°) derived from nicotinylacetic ester and 1,2-dichloroethyl ethyl ether in aqueous ammonia.[415]

Disubstituted

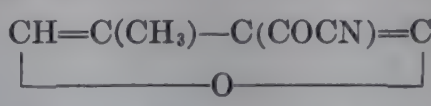
2,5-Dimethyl-3-furoic acid: (earlier names were pyrotritaric acid and uvinic acid); 2,3,5-$C_4HO(CH_3)(COOH)(CH_3)$; m.p. 134–135°, 136–137°. This acid was first obtained by Wislicenus and Stadnicki[436] as a product of the dry distillation of tartaric acid, and was named by them pyrotritaric acid. Later, Böttinger[437, 438, 439, 440] (see also [441, 442, 418]) isolated the same product by decomposition of pyruvic acid on heating with barium hydroxide or sodium acetate, and referred to it as "uvinic acid." The structure of the acid was correctly assigned by Paal[400] who derived it from α-acetonylacetoacetic ester (from chloroacetone and ethyl sodioacetoacetate) on warming with fuming hydrochloric acid (see also [443]) and also from 2,3-diacetosuccinic ester by similar ring closure (see also [444]). Hurd and Wilkinson[401] employed an unequivocal synthesis whereby 2,5-dimethylfuran was acetylated and the resulting ketone was subjected to the haloform reaction. In addition to these methods of preparation, the acid has also been obtained by partial decarboxylation of 2,5-dimethyl-3,4-furandicarboxylic acid,[444, 445, 446, 422, 447, 448] or of 5-carboxymethyl-2-methyl-3-furoic acid.[422, 327] Derivatives: **methyl ester,** b.p. 198°; **ethyl ester,** b.p. 214°, 99–101° (14 mm.); d_4^{20} 1.0537; n_D^{20} 1.46897[447, 327]; **acid chloride,** b.p. 87–89° (15 mm.)[448]; **amide,** m.p. 125° (from EtOH), 135° (from HOH)[449]; **α-naphthalide,** m.p. 148°[448]; **hydrazide,** m.p. 136–136.6°[314, 317]; **azide,** m.p. 24–25°[314]; **nitrile,** b.p. 183–183.5°, formed by ring closure of 3-cyano-2,5-hexandione (cyanoacetonylacetone) on heating with hydrogen chloride.[449]

2,4-Dimethyl-3-furoic acid: 2,3,4-$C_4HO(CH_3)(COOH)(CH_3)$; m.p. 125–126°, b.p.

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[436] Wislicenus and Stadnicki, *Ann.*, **146,** 306 (1868).
[437] Böttinger, *Ann.*, **172,** 239 (1874).
[438] Böttinger, *Ber.*, **9,** 670 (1876).
[439] Böttinger, *Ann.*, **188,** 293 (1877).
[440] Böttinger, *Ber.*, **13,** 1969 (1880).
[441] Fittig, *Ann.*, **267,** 186 (1892).
[442] Wolff, *Ann.*, **317,** 23 (1901).
[443] Korschen, *Ber.*, **37,** 2183 (1904).
[444] Harrow, *Ann.*, **201,** 141 (1880).
[445] Knorr, *Ber.*, **17,** 2863 (1884).
[446] Dietrich and Paal, *Ber.*, **20,** 1077 (1887).
[447] Knorr and Cavallo, *Ber.*, **22,** 153 (1889).
[448] Gilman and Burtner, *Rec. trav. chim.*, **51,** 667 (1932).
[449] Justoni, *Gazz. chim. ital.*, **71,** 375 (1941); *C. A.*, **36,** 7002 (1942).

131° (12 mm.). Prepared by the action of aqueous bromine, in the cold, on isodehydracetic acid (dimethylcoumalic acid)[450, 448]; by condensation of acetoacetic ester with chloroacetone in the presence of ammonia[406, 401] (see also [408]); and by partial decarboxylation of 4-methyl-2-carboxymethyl-3-furoic acid.[417, 451]
Derivatives: **ethyl ester,** b.p. 52° (0.8 mm.), 100–101° (20 mm.); n_D^{20} 1.4681[314, 408]; **acid chloride,** b.p. 78–79° (11 mm.)[451]; **anilide,** m.p. 135–136°, which with PCl_5 gave rise to the **phenylimido chloride,** b.p. 132° (0.7 mm.)[451]; **hydrazide,** m.p 144–145°[314]; **nitrile,** b.p. 66° (11 mm.).[451] Treatment of the acid chloride with hydrogen cyanide produced the **carboxylic cyanide,**



b.p. 91° (11 mm.), which was reduced with zinc and acetic acid to the cyanohydrin of 2,4-dimethyl-3-furaldehyde.[451]

4,5-Dimethyl-3-furoic acid: 3,4,5-$C_4HO(COOH)(CH_3)(CH_3)$; m.p. 130–131°, by partial decarboxylation of 4,5-dimethyl-2,3-furandicarboxylic acid.[334]

5-Ethyl-2-methyl-3-furoic acid: 2,3,5-$C_4HO(CH_3)(COOH)(C_2H_5)$; m.p. 98.5–99°, by decarboxylation of 5-(1-carboxyethyl)-2-methyl-3-furoic acid, and also by ring closure of α-acetyl-β-propionylpropionic ester which produces the ethyl ester, b.p. 98–104° (11 mm.)[424] (see also [349]).

4-Ethyl-2-methyl-3-furoic acid: 2,3,4-$C_4HO(CH_3)(COOH)(C_2H_5)$; m.p. 105–106°, by decarboxylation of 4-ethyl-2-carboxymethyl-3-furoic acid.[424]

2,5-Diethyl-3-furoic acid: 2,3,5-C_4HO—$(C_2H_5)(COOH)(C_2H_5)$; b.p. *ca.* 215°, by hydrolysis of the nitrile (not isolated), obtained by cyclization of 4-cyano-3,6-octandione with concentrated HCl.[452]

5-Phenyl-2-methyl-3-furoic acid: 2,3,5-$C_4HO(CH_3)(COOH)(C_6H_5)$; m.p. 180–181°, derived from α-phenacylacetoacetic ester (see footnote, p. 561). Decomposed on heating into 5-phenyl-2-methylfuran[400, 403a] (see also [453]). What may be the N-methylamido derivative (m.p. 147–148°) of the acid was reported by March.[454, 455]

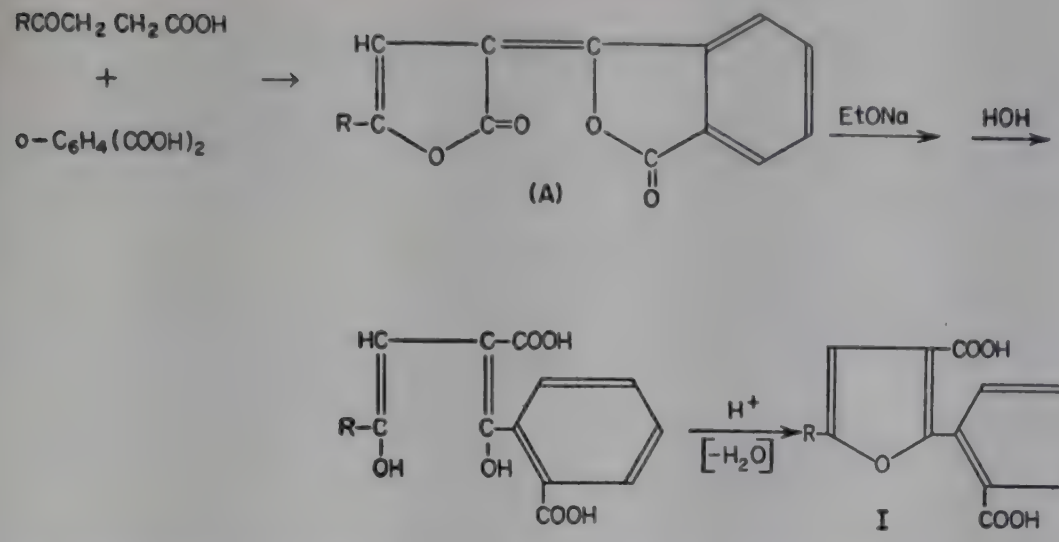
5-*p*-Methoxyphenyl-2-methyl-3-furoic acid: 2,3,5-$C_4HO(CH_3)(COOH)(C_6H_4OMe\text{-}p)$; m.p. 204.5–206°. **Methyl ester,** m.p. 81.5–82°; **ethyl ester,** m.p. 66–67°; obtained by ring closure of *p*-methoxyphenacylacetoacetic ester on heating with alcoholic hydrogen chloride.[414]

2-Phenyl-5-methyl-3-furoic acid: 2,3,5—$C_4HO(C_6H_5)(COOH)(CH_3)$; m.p. 147–148°, obtained as the ester on heating α-acetonylbenzoylacetic ester alone or with hydrochloric acid[403b] (see also [456]).

2-*o*-Carboxyphenyl-5-methyl-3-furoic acid: (I below, where R = CH_3); m.p. 238–240°, derived from levulinic acid and *o*-phthalic acid. The reaction is presumed to occur by way of the substituted γ-crotonolactone (A) which is split with sodium ethoxide and then closed by heating with alcoholic sulfuric acid.[457]

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[450] Feist, *Ber.*, **26,** 747 (1893).
[451] Reichstein and Zschokke, *Helv. Chim. Acta*, **15,** 1105 (1932).
[452] Justoni and Terruzzi, *Gazz. chim. ital.*, **78,** 166 (1948); *C. A.*, **43,** 2937 (1949).
[453] Kühn, *J. prakt. Chem.*, **156,** 103 (1940).
[454] March, *Compt. rend.*, **134,** 843 (1902).
[455] March, *Ann. chim. phys.*, (7), **26,** 295 (1902).
[456] Colefax, *J. Chem. Soc.*, **59,** 190 (1891).
[457] Borsche, *Ber.*, **47,** 2708 (1914).



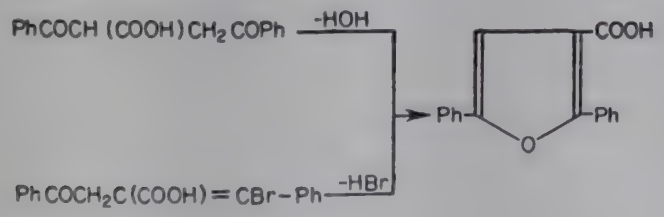
2-*o*-Carboxyphenyl-5-phenyl-3-furoic acid: (I above, where R = C_6H_5); m.p. 263°, as in the preceding case from 3-benzoylpropionic acid and *o*-phthalic acid.[457]

2-*o*-Carboxyphenyl-5-*p*-tolyl-3-furoic acid: (I above, where R = $C_6H_4CH_3$-*p*); m.p. 265–266°; as in the preceding case from 3-*p*-toluylpropionic acid and *o*-phthalic acid; **dimethyl ester,** m.p. 103°; **diethyl ester,** m.p. 76–77°.[457]

2-*o*-Carboxyphenyl-5-*p*-methoxystyryl-3-furoic acid: (I above, where R = CH_3O—C_6H_4—CH=CH-*p*); m.p. 268–269°; as in the preceding case from 5-*p*-methoxybenzylidenelevulinic acid and *o*-phthalic acid; **dimethyl ester,** m.p. 112°.[457]

5-(2-Naphthyl)-2-ethyl-3-furoic acid: 2-$C_{10}H_7$—C(—O—)=CH—C(COOH)=C—C_2H_5; m.p. 196°; **ethyl ester,** m.p. 61–62°, obtained by ring closure of α-(2-naphthacyl)propionylacetic ester on distillation[458] (see also [459]).

2,5-Diphenyl-3-furoic acid: 2,3,5-$C_4HO(C_6H_5)(COOH)(C_6H_5)$; m.p. 217°. Formed in almost quantitative yield by treatment of α-phenylacetylenylbenzoyl acetic acid or α-phenacylbenzoylacetic ester with alcoholic hydrochloric acid.[460] Also derived from α-phenacyl-β-bromocinnamic acid on heating or by the action of alkali.[461] **Esters:** methyl, m.p. 63°[461]; ethyl, m.p. 81–82°.[460, 461] **Acid chloride,** m.p. 95–97°, converted into 2,5-diphenyl-3-furyl diazomethyl ketone (m.p. 136.5–138°) on treatment with diazomethane[462] (see also [463]).



Trisubstituted

2,4,5-Trimethyl-3-furoic acid: 2,3,4,5-$C_4O(CH_3)(COOH)(CH_3)(CH_3)$; m.p. 131–132°, by partial decarboxylation of 4,5-dimethyl-2-carboxymethyl-3-furoic acid.[349]

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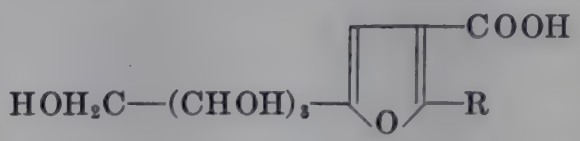
[458] Weidlich and Daniels, *Ber.*, **72,** 1590 (1939).
[459] Weidlich and Meyer-Delius, *Ber.*, **72,** 1941 (1939).
[460] Kapf and Paal, *Ber.*, **21,** 1485, 3053 (1888).
[461] Thiele and Mayr, *Ann.*, **306,** 171 (1899).
[462] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70,** 1359 (1948).
[463] Perkin and Schloesser, *J. Chem. Soc.*, **57,** 944 (1890).

Also prepared as the ethyl ester (b.p. 100–105° (12 mm.)) by ring closure of 2,3-diacetobutyric ester.[349]

2,4,5-Triphenyl-3-furoic acid: 2,3,4,5-$C_4O(C_6H_5)(COOH)(C_6H_5)(C_6H_5)$; m.p. 257–258°, from triphenyl-halofuran by the action of *n*-butyllithium followed by carbonation. **Methyl ester,** m.p. 123.5–124°.[464]

Hydroxyalkyl-3-furoic Acids.

5-Tetrahydroxybutyl-2-methyl-3-furoic acid and related acids:



Compounds of this type were obtained by condensation of glucose with acetoacetic ester (R = CH_3; m.p. 160–161°), with β-ketovaleric ester (R = C_2H_5), with β-ketocaproic ester (R = C_3H_7), with benzoylacetic ester (R = C_6H_5; m.p. 176–177°), and with β-ketoglutaric ester (R = CH_2COOH; free dicarboxylic acid, m.p. 162–163°; diethyl ester, m.p. 128–130°).[425, 426, 427, 428, 429, 465, 430] Mannose reacts similarly to glucose, but no similar reaction has been noted with galactose, fructose, xylose, maltose or lactose.

Acylfuran-3-carboxylic Acids.

5-Formyl-3-furoic acid (4-carboxyfurfural): 3,5-$C_4H_2O(COOH)(CHO)$; m.p. 158–159°, by hydrolysis of the **methyl ester** (m.p. 93.5°; phenylhydrazone, m.p. 114–115°) obtained by catalytic reduction of 4-carbomethoxy-2-furoyl chloride over a palladium-barium sulfate catalyst. The hydrazone derivative melts at 145–146°.[433]

5-Formyl-2-methyl-3-furoic acid: 2,3,5-$C_4HO(CH_3)(COOH)(CHO)$; m.p. 176°, by oxidation of 5-tetrahydroxybutyl-2-methyl-3-furoic acid with periodic acid[430] or with lead tetracetate.[425] For condensation with angelica lactone, see Russell, Todd and Waring.[466] **Ethyl ester,** m.p. 59°; **phenylhydrazone,** m.p. 100°; **2,4-dinitrophenylhydrazone,** m.p. 234° (dec.); **semicarbazone,** m.p. 223°; **dimedon,** m.p. 183–184°.

5-Formyl-2-propyl-3-furoic acid: 2,3,5-$C_4HO(C_3H_7)(COOH)(CHO)$; obtained as the **ethyl ester** (phenylhydrazone, m.p. 82–83°; semicarbazone, m.p. 173°) by oxidation of 5-tetrahydroxybutyl-2-propyl-3-furoic ester with lead tetracetate.[429]

5-Formyl-2-phenyl-3-furoic acid: 2,3,5-$C_4HO(C_6H_5)(COOH)(CHO)$; m.p. 145–147°, **ethyl ester,** m.p. 76° (phenylhydrazone, m.p. 124–126°; semicarbazone, m.p. 170–171°) by oxidation of 5-tetrahydroxybutyl-2-phenyl-3-furoic acid or ester with lead tetracetate.[427]

5-Formyl-2-carboxymethyl-3-furoic acid: 2,3,5-$C_4HO(CH_2COOH)(COOH)(CHO)$; as the **diethyl ester** (phenylhydrazone, m.p. 96–97°; 2,4-dinitrophenylhydrazone, m.p. 168–170°; semicarbazone, m.p. 180–182°) by oxidation of 5-tetrahydroxybutyl-2-carboxymethyl-3-furoic acid diethyl ester with lead tetracetate.[427]

2,5-Dimethyl-4-acetyl-3-furoic acid: 2,3,4,5—$C_4O(CH_3)(COOH)(COCH_3)(CH_3)$; m.p. 151.5–152°. **Phenylhydrazone,** decomposes at 185–187° with loss of carbon dioxide

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[464] Gilman and Melstrom, *J. Am. Chem. Soc.*, **68**, 103 (1946).

[465] Gonzalez and Sequeiros, *Anales fis. y quim. Madrid*, **41**, 1479 (1945); *C. A.*, **43**, 5391 (1949).

[466] Russell, Todd and Waring, *Biochem. J.*, **45**, 530 (1949).

and formation of 2,5-dimethyl-3-acetylfuran phenylhydrazone, m.p. 137°. The **oxime** derivative is more stable, m.p. 198–199°.[467, 468]

5-Acetonyl-2-methyl-3-furoic acid: $2,3,5\text{-}C_4HO(CH_3)(COOH)(CH_2COCH_3)$; m.p. 121–122°; by heating acetylacetone with sodium succinate in acetic anhydride.[469]

2,5-Diphenyl-4-benzoyl-3-furoic acid:

$$2,3,4,5\text{-}C_4O(C_6H_5)(COOH)(COC_6H_5)(C_6H_5)$$

m.p. 142–143°, derived from *sym.*-tetrabenzoylethylene by the action of light, followed by ring closure.[470]

3-Carboxyfurylacetic Acids and Homologous Acids.

2-Carboxymethyl-3-furoic acid (3-carboxy-2-furylacetic acid);

$$2,3\text{-}C_4H_2O(CH_2COOH)(COOH)$$

m.p. 217–218°. The **diethyl ester,** b.p. 86–90° (2 mm.), by condensation of β-ketoglutaric ester with 1,2-dichloroethyl ethyl ether. Using aqueous ammoniacal medium, the yield is 10–11 per cent which is increased to 18 per cent by conducting the reaction in dilute sodium hydroxide[81] (see also [416, 471, 472]).

4-Methyl-2-carboxymethyl-3-furoic acid (4-methyl-3-carboxy-2-furylacetic acid); $2,3,4\text{-}C_4HO(CH_2COOH)(COOH)(CH_3)$; m.p. 196.5°. The **diethyl ester,** b.p. 109–110° (0.5 mm.), 160° (12 mm.), 177–179 (25 mm.), obtained in good yield from β-ketoglutaric ester and chloroacetone in the presence of ammonia.[417, 473, 332, 451, 333, 314] Partial saponification gives the **monoester,** ethyl 4-methyl-2-carboxymethyl-3-furoate, m.p. 109°.[417] **Bisdiethylamide,** b.p. 158–160° (0.65 mm.).[474] The **diethyl ester,** by the action of ethyl nitrite and sodium ethoxide, is converted into the **hydroximino ester,** m.p. 83–84°, which on saponification produces the corresponding dicarboxylic acid, $HC{=}C(CH_3){-}C(COOH){=}C{-}C(NOH)COOH$, m.p. 187–191° (dec.).[451, 333] Treatment of the latter with acetic anhydride gives rise to 4-methyl-3-carboxy-2-furonitrile (see p. 576).

4-Ethyl-2-carboxymethyl-3-furoic acid:

$$2,3,4\text{-}C_4HO(CH_2COOH)(COOH)(C_2H_5)$$

m.p. 192–193° (dec.). Obtained as the **diethyl ester** (b.p. 110–116° (0.25 mm.)) by condensation of chloromethyl ethyl ketone with β-ketoglutaric ester in the presence of ammonia.[424]

4,5-Dimethyl-2-carboxymethyl-3-furoic acid:

$$2,3,4,5\text{-}C_4O(CH_2COOH)(COOH)(CH_3)(CH_3)$$

m.p. 211° (dec.); obtained, as the **diethyl ester** (b.p. 124° (0.24 mm.)), by the Feist

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[467] Magnanini, *Gazz. chim. ital.*, **18,** 116 (1888).

[468] Magnanini and Scheidt, *Gazz. chim. ital.*, **22, I,** 436 (1892).

[469] Stefanovskaya, Dorofeev and Trefil'ev, *J. Gen. Chem. U. S. S. R.*, **11,** 518 (1941); *C. A.*, **35,** 6952 (1941).

[470] Schmid, Hochweber and Halban, *Helv. Chim. Acta*, **30,** 423, 1135 (1947).

[471] Martin, Baumann and Gysin, (to Geigy A.-G), U. S. Patent 2,317,286 (1943); *C. A.*, **37,** 5830 (1943).

[472] Geigy, A.-G., British Patent 545,609 (1942); *C. A.*, **37,** 2014 (1943).

[473] Trefil'ev, *Ber.*, **41,** 2543 (1908).

[474] Geigy, A.-G., Swiss Patent 235,938 (1945); *C. A.*, **43,** 4301 (1949).

synthesis involving condensation of β-ketoglutaric ester with methyl chloroethyl ketone in the presence of ammonia.[349, 334]

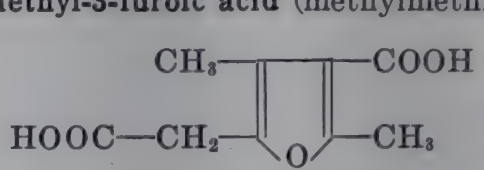
5-Carboxymethyl-2-methyl-3-furoic acid (methronic acid):

$$2,3,5\text{-}C_4HO(CH_3)(COOH)(CH_2COOH)$$

m.p. 204, 207°. Prepared by warming ethyl acetoacetate and sodium succinate in acetic anhydride[475, 473, 418] (see also [421, 419, 420]). It is also obtained by condensation of acetoacetic ester with glyoxal in the presence of zinc chloride[423] (see also [422]).

A variety of derivatives have been described.[327, 423, 471, 472, 473, 476] The amido derivatives are reported to be of considerable therapeutic value, particularly with respect to their analeptic properties.

5-Carboxymethyl-2,4-dimethyl-3-furoic acid (methylmethronic acid):



m.p. 198°; **diethyl ester,** b.p. 175–176° (*ca.* 20 mm.). Obtained by condensation of acetoacetic ester and sodium pyrotartrate in acetic anhydride.[420]

5-Carboxymethyl-2-phenyl-3-furoic acid:

$$2,3,5\text{-}C_4HO(C_6H_5)(COOH)(CH_2COOH)$$

m.p. 192–193°. Prepared by condensation of benzoylacetoacetic ester with sodium succinate in acetic anhydride[420] (see also [456, 476a]).

5-(1-Carboxyethyl)-2-methyl-3-furoic acid:

$$2,3,5\text{-}C_4HO(CH_3)(COOH)[CH(CH_3)COOH]$$

m.p. 200–201°, by condensation of methylsuccinic acid with acetoacetic ester in acetic anhydride[424] (see also [420]).

Polycarboxyfurans

In this section we are concerned with those derivatives of furan which possess two or more carboxyl groups linked directly to the nucleus. The complete series has been described: four isomeric furandicarboxylic acids, the two furantricarboxylic acids, and furantetracarboxylic acid.

Furandicarboxylic Acids

2, 5-Furandicarboxylic Acid. This product, known in the early literature as dehydromucic acid, was first described by Fittig and Heinzelmann[16] (see also [15]) who derived it from mucic acid by the action of fuming hydrobromic acid (see also [17]). Shortly thereafter, Seelig[18] showed that hydrochloric acid could be used in place of hydrobromic acid. Klinkhardt[4] later

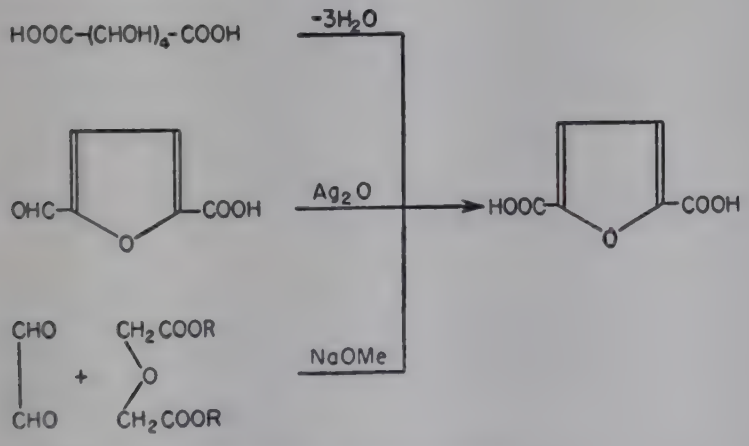
[475] Trefil'ev, *Ber.*, **39,** 1859 (1906).

[476] Robinson and Thompson, *J. Chem. Soc.*, **1938,** 2009.

[476a] Trefil'ev, *J. Russ. Phys. Chem. Soc.*, **40,** 1341 (1908); *C. A.*, **3,** 636 (1909); Trefil'ev and Mangubi, *Ibid.*, **41,** 875 (1909); *Chem. Centr.*, **1909, II,** 1874.

recommended a mixture of the two halogen acids. Concentrated sulfuric acid was employed by Yoder and Tollens,[107] whereas others[6, 7] obtained the desired product in low yield by merely heating mucic acid, alone or in aqueous solution. The report of Schmitt and Cobenzl[5] that potassium 2,5-furandicarboxylate is obtained by heating potassium mucate in an atmosphere of hydrogen could not be confirmed by Phelps and Hale.[477]

Faced with the necessity of preparing 2,5-furandicarboxylic acid in fairly substantial amount, Hill[19] found that refluxing in concentrated hydrobromic acid effected a reasonably rapid rate of conversion of mucic acid; that under similar conditions, saccharic acid was even more rapidly transformed to the furandicarboxylic acid. In the latter instance, the product yield was 25–30 per cent of the weight of saccharic acid (as the acid potassium salt) taken, and this yield was improved by employing yet stronger hydrobromic acid (sp. gr. 1.56).[477] Saccharic acid had earlier been used as a precursor of 2,5-furandicarboxylic acid by Sohst and Tollens[9] and by Schrötter.[478] Related carbohydrate materials which have been employed include isosaccharic acid[11] and its isomer, chondrosic acid.[12] The furan acid has also been isolated from human urine as a result of ingestion of glucuronic or galacturonic acids.[479, 480, 481] It is formed in quantitative yield by treatment of 5-formyl-2-furoic acid with alkaline silver oxide,[223] and in low yield by oxidation of 5-(hydroxymethyl)furfural and its derivatives[360, 361, 356, 380, 370] or by condensation of glyoxal with dimethyl diglycollate in the presence of sodium methoxide.[482]

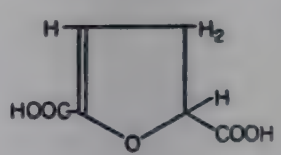


[477] Phelps and Hale, *Am. Chem. J.*, **25**, 445 (1901).
[478] Schrötter, *Monatsh.*, **9**, 443 (1888); *Chem. Centr.*, **1888, II**, 1092.
[479] Flaschenträger, Cagianut and Meier, *Helv. Chim. Acta*, **28**, 1489 (1945).
[480] Flaschenträger, Cagianut and Ryffel, *Helv. Physiol. Pharmacol. Acta*, **2, C**, 43 (1944); *C. A.*, **40**, 628 (1946).
[481] Flaschenträger and Bernhard, *Z. physiol. Chem.*, **246**, 124 (1937); *C. A.*, **31**, 4709 (1937).
[482] Hoehn, *Iowa State Coll. J. Sci.*, **11**, 66 (1936).

2,5-Furandicarboxylic acid is sparingly soluble in water. It sublimes readily, and on rapid heating is decomposed with loss of carbon dioxide and formation of 2-furoic acid. It exhibits very pronounced stability toward acidic reagents,[483] and strongly resists substitution by halogens (see Chapter 3). Unlike 2-furoic acid, it is readily reduced by sodium amalgam.[16, 18, 478, 484] Hill[19, 485] (see also [477]) investigated this reaction carefully, and showed that when the reduction is carried out at 0°, (using carbon dioxide to combine with the liberated sodium hydroxide), two atoms of hydrogen are added giving rise to dihydrofuran-2,5-dicarboxylic acid (α-form, m.p. 149–150°). Treatment with alkali converts this product to an isomeric β-form, m.p. 178–179°. The latter is separable, by means of the cinchonine salts, into two optically active acids of opposite rotation. More prolonged alkali treatment of the α-, or the β-acids, produces yet another isomeric form, the γ-form (dec. between 190–200°), which is similarly separable into two optically active components. Hill concluded that the α- and β-forms possessed the 2,5-dihydro configuration, I, with two asymmetric carbon atoms which should permit an unresolvable *cis* form (the α- or *meso*-acid) and two resolvable (*cis - trans*) forms (the β-acid being the racemic, or inactive combination of these). He further postulated that the isomeric γ-acid was the racemic modification of 2,3-dihydrofuran-2,5-dicarboxylic acid, II. Whereas the α- and β-acids are not affected by further treatment with sodium amalgam, the γ-acid is converted into two stereoisomeric forms of tetrahydrofuran-2,5-dicarboxylic acid, m.p. 94–95° and 124°.



I



II

Derivatives of 2,5-furandicarboxylic acid:

Esters: monomethyl, m.p. 201–202°; monoethyl, m.p. 148–149°[477]; dimethyl, m.p. 112°, b.p. 154–156° (15 mm.); diethyl, m.p. 47°, b.p. 167–168° (15 mm.); di-*n*-propyl, m.p. 21–21.5°, b.p. 177–178° (5 mm.); di-*i*-propyl, m.p. 42–42.5°, b.p. 156–159° (13 mm.); di-*n*-butyl, m.p. 37–38°, b.p. 186–190° (13 mm.); di-*i*-butyl, m.p. 88°, b.p. 172–174° (13 mm.); di-*i*-pentyl, m.p. 37.5°, b.p. 207–211° (18 mm.)[107]; diphenyl, m.p. 138.5°.[115] **Acid chloride,** m.p. 80°.[4] **Monoamide,** m.p. 283°[477, 343]; **diamide,** m.p. >220°[158]; **dianilide,** m.p. 227–228°[477]; **N,N′-dimethyl-2,5-furandicarboxamide,** m.p.

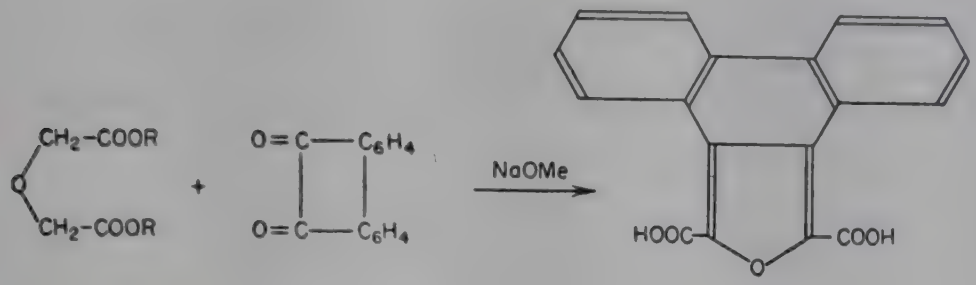
[483] Gilman and Young, *Rec. trav. chim.*, **51**, 761 (1932).

[484] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany, 1930.

[485] Hill and Wheeler, *Am. Chem. J.*, **25**, 463 (1901).

97°.[158] **2,5-Furodihydroxamic acid,** m.p. >250°.[158] **Sulfanilamide derivatives** are described by Jain, Iyer and Guha.[486, 487]

3,4-Diphenyl-2,5-furandicarboxylic acid: m.p. 303° (dec.), isolated from the mixture of products resulting from condensation of benzil with diglycollic methyl ester in the presence of sodium methoxide. **Methyl ester,** m.p. 209–210°; **ethyl ester,** m.p. 129.5–130°. On heating the acid above its melting point, carbon dioxide was evolved with formation of 3,4-diphenylfuran.[357] When 9,10-phenanthraquinone is substituted for benzil in the above synthesis, there is obtained the condensed ring product, phenanthrofurandicarboxylic acid, III (dihydrate, dec. 280°).[358]



III

2,3-Furandicarboxylic Acids. 2,3-Furandicarboxylic acid has been obtained from several natural sources by oxidative degradation using alkaline hydrogen peroxide. These sources include pimpinellin from the root of *Pimpinella saxifraga*,[488, 489] ficusin from the leaves of *Ficus carica*,[490] isopsoralene from the fatty oil of the seeds of *Psoralea corylifolia*,[491] derridenone, an analog of rotenone from derris root,[492] byakangelicol, a constituent of umbelliferene,[493] and angelicin from the root of *Angelica archangelica L.*[494] (see also [495]). It has also been synthesized from 3-formyl-2-furoic acid by oxidation,[89] and from 2-carboxymethyl-3-furoic acid by conversion to the isonitroso derivative, dehydration and partial decarboxylation to 3-carboxy-2-furonitrile and subsequent saponification.[81] The latter procedure (see p. 564) was also employed for the preparation of the appropriate homologs from 4-methyl- and 4,5-dimethyl-2-carboxymethyl-3-furoic acids.[338, 332, 334]

[486] Jain, Iyer and Guha, *Science and Culture*, **11**, 270 (1945); *C. A.*, **40**, 2125 (1946).
[487] Jain, Iyer and Guha, *J. Indian Chem. Soc.*, **24**, 177 (1947); *C. A.*, **43**, 2597 (1949).
[488] Wessely and Nadler, *Monatsh.*, **60**, 141 (1932); *C. A.*, **26**, 4603 (1932).
[489] Wessely and Dinjaski, *Monatsh.*, **64**, 131 (1934); *C. A.*, **28**, 6435 (1934).
[490] Okahara, *Bull. Chem. Soc. Japan*, **11**, 389 (1936); *C. A.*, **30**, 7575 (1936).
[491] Jois and Manjunath, *Ber.*, **69**, 964 (1936).
[492] Meyer, *Rec. trav. chim.*, **58**, 1119 (1939).
[493] Noguti and Kawakami, *J. Pharm. Soc. Japan*, **58**, 1052 (1938); *C. A.*, **33**, 2513 (1939).
[494] Späth and Pesta, *Ber.*, **67**, 853 (1934).
[495] Späth and Gruber, *Ber.*, **74**, 1492 (1941).

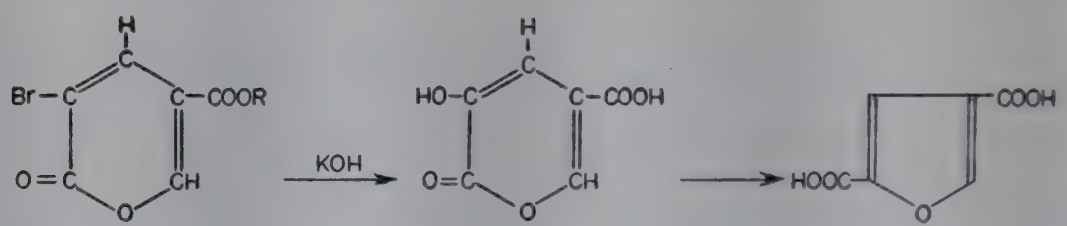
2,3-Furandicarboxylic acid: m.p. 225°. **Dimethyl ester,** m.p. 36°, 37°[89, 491]; **diethyl ester,** m.p. 34°[89]; **2-carboxy-3-furonitrile,** m.p. 183°[89]; **3-carboxy-2-furonitrile,** m.p. 225°[81]; **3-carboxy-2-furanilide,** m.p. 169–170°.[89] Nitration and bromination of the dimethyl ester proceeds as expected with introduction of the appropriate substituent at the open alpha nuclear position.[432]

4-Methyl-2,3-furandicarboxylic acid: m.p. 233° (dec.). **Monomethyl ester** (3-carbomethoxy), m.p. 119.5°[432]; **monoamide** (2—$CONH_2$), m.p. 228–230°[332]; **4-methyl-3-carboxy-2-furonitrile,** m.p. 203–4°[333, 334] (methyl ester, m.p. 49°).[496]

4,5-Dimethyl-2,3-furandicarboxylic acid: m.p. 252° (dec.). The **2-nitrile,** m.p. 156–157°, b.p. 159° (0.8 mm.).[334]

5-Carboxymethyl-4-methyl-2,3-furandicarboxylic acid: m.p. 251–252°. In connection with studies relating to the structure of usninic acid and its degradation products, usnetinic and pyrousninic acids, were oxidized with hydrogen peroxide with formation of this derivative of 2,3-furandicarboxylic acid. **Trimethyl ester,** b.p. 162° (2 mm.)[346] (see also [497]).

2,4-Furandicarboxylic Acid and Related Acids. By the action of potassium hydroxide, 3-bromocoumalic ester is converted into 2,4-furandicarboxylic acid in practically quantitative yield[498, 80] (see also [499]). Homologous



acids are obtained similarly from substituted 3-bromocoumalic acids,[450, 500] and also by oxidation of the 2-alkyl-5-tetrahydroxybutyl-3-furoic acids (p. 570) derived by condensation of glucose with β-keto esters.

2,4-Furandicarboxylic acid: m.p. 266°. **Dimethyl ester,** m.p. 106°, 109–110°.[501, 498]

4-Carbomethoxy-2-furoic acid, m.p. 132.5° (acid chloride, m.p. 83–84°).[433]

5-Methyl-2,4-furandicarboxylic acid: m.p. 270–272°. By oxidation of 5-methyl-4-acetyl-2-furoic acid,[116] and of 5-tetrahydroxybutyl-2-methyl-3-furoic acid.[428, 425] **Dimethyl ester,** m.p. 53°, 61–62°[430, 438]; **acid chloride,** m.p. 25–26°, b.p. 133–135° (14 mm.)[428]; **diamide,** m.p. 210–211°[428]; **dianilide,** m.p. 196–197°.[428]

5-Propyl-2,4-furandicarboxylic acid: m.p. 260° (dec.). By oxidation of 5-tetrahydroxybutyl-2-propyl-3-furoic acid.[429]

5-*i*-Butyl-2,4-furandicarboxylic acid: sublimes 260° (dec.). By oxidation of 5-tetrahydroxybutyl-2-*i*-butyl-3-furoic acid.[429]

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[496] Bilton, Linstead and Wright, *J. Chem. Soc.*, **1937**, 922.
[497] Asahina, Yanagita and Kawamura, *Ber.*, **70**, 1500 (1937).
[498] Feist, *Ber.*, **34**, 1992 (1901).
[499] Pechmann, *Ann.*, **264**, 261 (1891).
[500] Buchner and Schröder, *Ber.*, **35**, 782 (1902).
[501] Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 555 (1933).

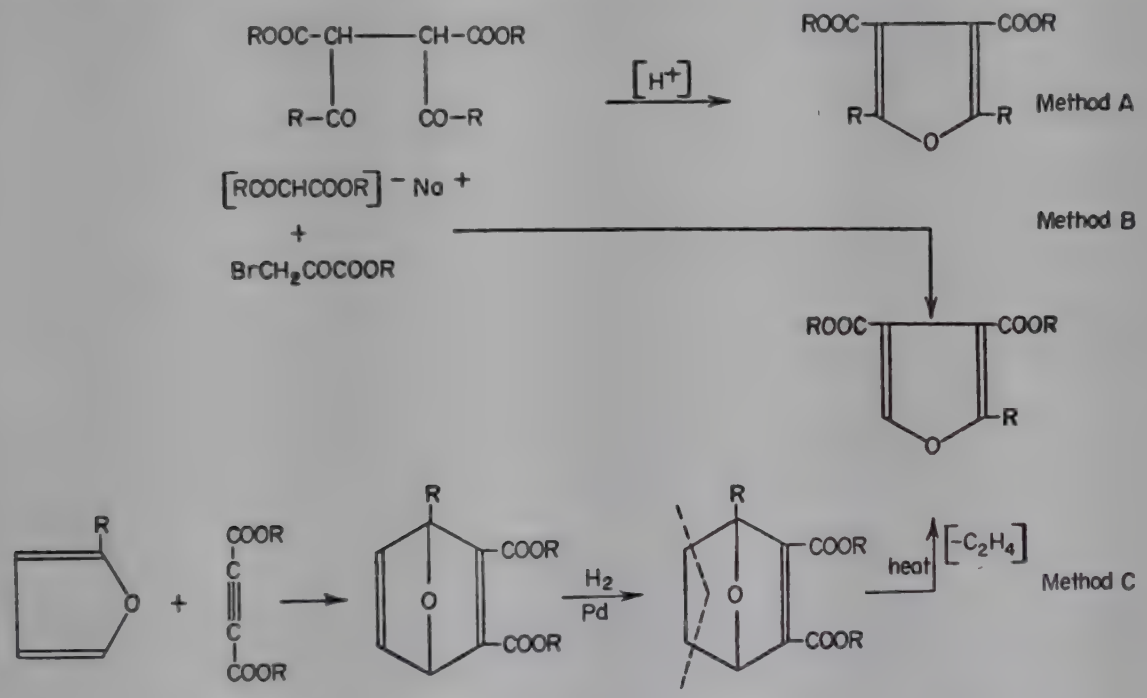
5-Phenyl-2,4-furandicarboxylic acid: m.p. 270–271°. By oxidation of 5-formyl-2-phenyl-3-furoic acid. **Diethyl ester,** m.p. 95–96°; **acid chloride,** m.p. 68–72°; **diamide,** m.p. 206–208°; **dianilide,** m.p. 147–150°.[427]

3,5-Dimethyl-2,4-furandicarboxylic acid: m.p. *ca.* 260° (dec.); by the action of potassium hydroxide on 3-bromo-4,6-dimethylcoumalic acid.[450]

3-Phenyl-5-methyl-2,4-furandicarboxylic acid: m.p. 224° (dec.); from 3-bromo-4-phenyl-6-methylcoumalic ester by the action of potassium hydroxide.[500]

5-Carboxymethyl-2,4-furandicarboxylic acid: m.p. 238–240°. **Trimethyl ester,** m.p. 68–73°. By oxidation of 5-formyl-2-carboxymethyl-3-furoic acid.[427]

3,4-Furandicarboxylic Acid and Related Acids. 3,4-Furandicarboxylic acid is obtained by partial decarboxylation of furantetracarboxylic acid by way of the 2,3,4-tricarboxylic acid.[82, 396] For the preparation of the related alkyl and aryl substituted acids, three synthetic methods are available.

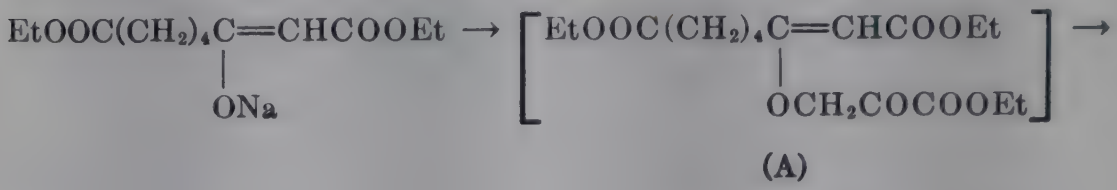


Method A involves cyclization of an α,β-diacylsuccinic ester. This was first achieved by Harrow,[444] who isolated the so-called "carbopyrotritaric acid" by heating diacetylsuccinic ester with sulfuric acid. A few years later, Paal[400] and Knorr[445] correctly formulated the product as a furan compound, 2,5-dimethyl-3,4-furandicarboxylic acid.

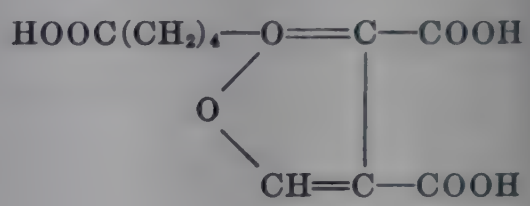
Method B involves condensation of bromopyruvic ester with the sodium derivative of a β-keto ester. Archer and Pratt[502] carried out this reaction with ethyl sodio-β-ketosuberate and obtained, on subsequent ring closure, 2-δ-carboxybutyl-3,4-furandicarboxylic acid, I. If C-alkylation of the ester had taken place in the first step, Archer's product would have been 5-δ-carboxybutyl-2,4-furandicarboxylic acid. To explain this result, Archer

[502] Archer and Pratt, *J. Am. Chem. Soc.*, **66**, 1656 (1944).

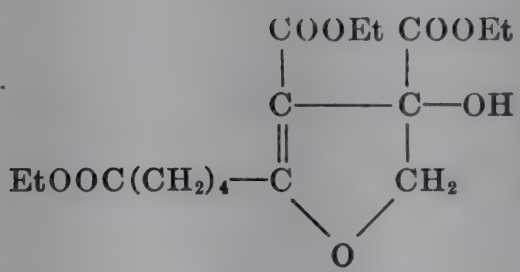
accepted an O-alkylation mechanism earlier postulated by Reichstein[82] (see also p. 582) for a related reaction. However, ring closure of the proposed O-alkylation intermediate (A) to a furan is considered unlikely, and it is believed that the initial reaction proceeds by way of aldolization to produce (B) or (C).[407]



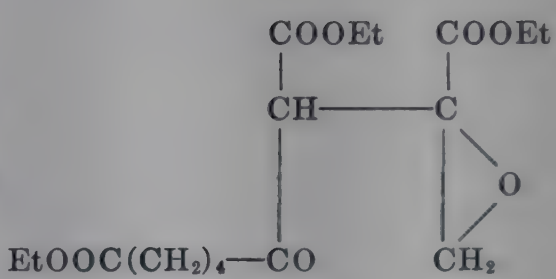
(A)



I



(B)



(C)

Method C is based on the observation of Alder and Rickert[503] that the partially hydrogenated adduct derived from a suitable furan compound and acetylenedicarboxylic ester is thermally unstable, and decomposes with loss of ethylene to form the appropriately substituted 3,4-furandicarboxylic acid. Hofmann[504, 505, 506, 507, 508] later employed this reaction rather extensively in connection with his synthetic work on substances related to biotin.

3,4-Furandicarboxylic acid: m.p. 217–218°. **Dimethyl ester,** m.p. 46°, b.p. 80° (0.3 mm.)[82]; **diamide,** m.p. 262° (dec.).[509] Acylation of the ester, in benzene, using acetic

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[503] Alder and Rickert, *Ber.*, **70,** 1354 (1937).
[504] Hofmann, *J. Am. Chem. Soc.*, **66,** 51 (1944).
[505] Hofmann, *J. Am. Chem. Soc.*, **67,** 421 (1945).
[506] Hofmann and Bridgwater, *J. Am. Chem. Soc.*, **67,** 738 (1945).
[507] Hofmann, Chen, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **69,** 191 (1947).
[508] Hofmann, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **71,** 1253 (1949).
[509] Stork, *J. Am. Chem. Soc.*, **67,** 884 (1945).

anhydride and stannic chloride, produces dimethyl 2-acetyl-3,4-furandicarboxylate, m.p. 108°.[510, 348] For the ultraviolet absorption spectrum, see Hofmann.[504]

Alkylated derivatives:

2-Methyl-3,4-furandicarboxylic acid: m.p. 230–231°; from the adduct obtained from 2-methylfuran and acetylenedicarboxylic ester according to method C.[503, 506, 511] **Dianilide,** m.p. 211–212°.[503] The **acid chloride,** b.p. 150–151° (25 mm.) was converted to the diazide, and thence to derivatives of 2-methyl-3,4-furandiamine[506, 504] (see also p. 192).

2,5-Dimethyl-3,4-furandicarboxylic acid: m.p. 230°, 232°.[445, 446] Derived from α,β-diacetylsuccinic ester according to method A[445, 447, 448] (see also [512, 513, 514, 515, 517]). **Esters:** monomethyl, m.p. 129°[447]; monoethyl, m.p. 83°[447] (see also [518]); dimethyl, m.p. 63–64°, b.p. 258°[447] (see also [519]); diethyl, b.p. 158–163° (20 mm.).[448] **Diamide,** m.p. 236°, 243–244° (dec.)[496, 520]; **bisdiethylamide,** m.p. 62°, b.p. 154–156° (0.4 mm.).[472, 521, 471] **4-Cyano-2,5-dimethyl-3-furoic acid,** m.p. 174°.[496] For reaction with the Grignard reagent, see Seka.[520]

2,5-Diethyl-3,4-furandicarboxylic acid: m.p. 153–154°, from α,β-dipropionylsuccinic ester according to method A.[522]

Arylated derivatives:

2-*p*-Chlorophenyl-3,4-furandicarboxylic acid: diethyl ester, m.p. 60–61°, b.p. 168–170° (0.2 mm.), obtained from the adduct of 2-*p*-chlorophenylfuran and ethyl acetylenedicarboxylate according to method C.[413]

2,5-Diphenyl-3,4-furandicarboxylic acid: m.p. 238°. **Diethyl ester,** m.p. 86°. Obtained from α,β-dibenzoylsuccinic ester according to method A[523, 513, 463] (see also [524]). When heated above its melting point, or in acetic anhydride, the dicarboxylic acid loses the elements of water to form a crystalline anhydride, I, m.p. 254–255°,[523, 513] which by reaction with urea and thiocarbanilide gives rise to the imide, II, and N-phenylimide, III, respectively.[525] For related cyclohydrazide derivatives, see Seka and Preissecker.[519]

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[510] Calloway, *Iowa State Coll. J. Sci.*, **9,** 141 (1934).

[511] Hofmann, (to Ciba Pharmaceutical Products Inc.), U. S. Patent 2,453,627 (1948); *C. A.*, **43,** 1441 (1949).

[512] Böttinger, *Ann.*, **208,** 122 (1881).

[513] Perkin and Calman, *J. Chem. Soc.*, **49,** 154 (1886).

[514] Paal and Hartel, *Ber.*, **30,** 1991 (1897).

[515] Trefil'ev and Razumov, *J. Russ. Phys. Chem. Soc.*, **61,** 699 (1929); *C. A.*, **23,** 4448 (1929).

[517] Korschun and Gounder, *Bull. soc. chim.*, **19,** 426 (1916).

[518] Roll and Timoshevskaya, *Nauch. Zapiski Khar'kov Poligraf. Inst.*, **1939,** No. 3, 117; *C. A.*, **37,** 3754 (1943).

[519] Seka and Preissecker, *Monatsh.*, **57,** 81 (1931); *C. A.*, **25,** 1826 (1931).

[520] Seka, *Ber.*, **57,** 1861 (1924).

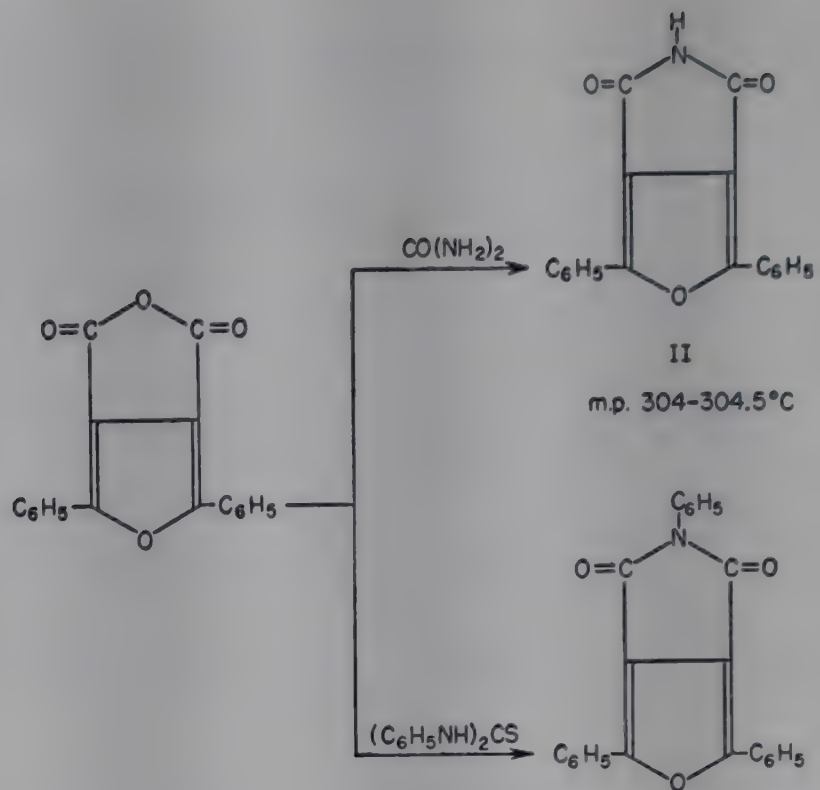
[521] Geigy, A.-G., Swiss Patent 235,939 (1945); *C. A.*, **43,** 4301 (1949).

[522] Woodward and Eastman, *J. Am. Chem. Soc.*, **68,** 2229 (1946).

[523] Perkin, *J. Chem. Soc.*, **47,** 262 (1885).

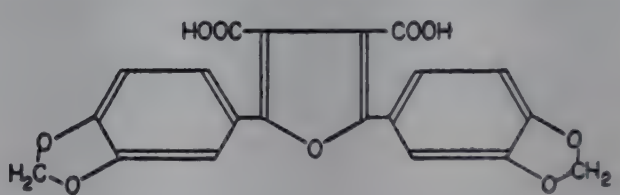
[524] Trefil'ev and Livanov, *J. Gen. Chem. U.S.S.R.*, **11,** 182 (1941); *C. A.*, **35,** 7960 (1941).

[525] Seka, *Ber.*, **58,** 1783 (1925).



2,5-Di-*p*-tolyl-3,4-furandicarboxylic acid: m.p. 264° (dec.). **Diethyl ester,** m.p. 118°, from α,β-di-*p*-toluylsuccinic ester according to method A.[526]

2,5-Bis(3,4-methylenedioxyphenyl)-3,4-furandicarboxylic acid:

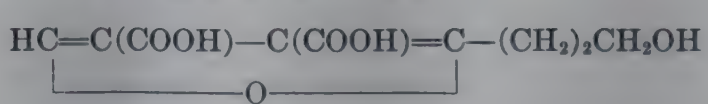


(m.p. 234°).

Diethyl ester, m.p. 118°, from α,β-dipiperonylsuccinic ester by method A. On heating the acid in acetic anhydride, it is converted into the inner anhydride, m.p. 277° (dec.). Attempted reduction (catalytic hydrogenation, Na in alcohol, Na-Hg, etc.) was unsuccessful.[527]

Hydroxyalkylfuran-3,4-dicarboxylic acids.

2-(3-Hydroxypropyl)-3,4-furandicarboxylic acid:



m.p. 161–162°. **Diethyl ester,** b.p. 146–152° (0.02 mm.), from 3-(2-furyl)-1-propanol and ethyl acetylenedicarboxylate according to method C. The dicarboxyfurylpropyl acetate melts at 70–72°.[507, 528]

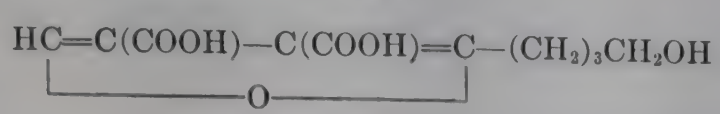
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[526] Coulson, *J. Chem. Soc.*, **1934**, 1406.

[527] Bruchhausen and Gerhard, *Ber.*, **72**, 830 (1939).

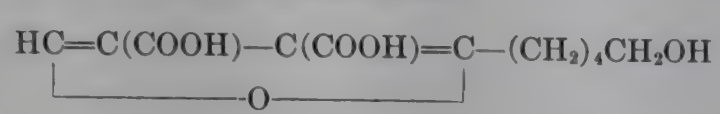
[528] Hofmann, (to Ciba Pharmaceutical Products Inc.), U. S. Patent 2,527,421 (1950).

2-(4-Hydroxybutyl)-3,4-furandicarboxylic acid:



m.p. 126–127°. **Diethyl ester,** b.p. 156–161°. (0.02 mm.), from 4-(2-furyl)-1-butanol and acetylenedicarboxylic ester according to method C. The dicarboxyfurylbutyl acetate, m.p. 89–90°.[507, 528]

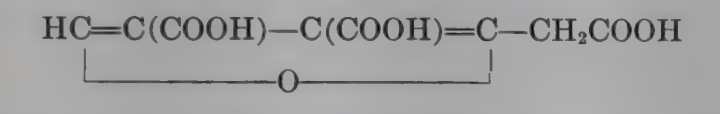
2-(5-Hydroxypentyl)-3,4-furandicarboxylic acid:



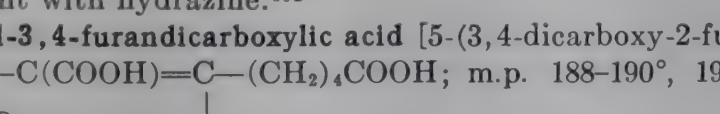
m.p. 124–126°. **Diethyl ester,** b.p. 174–178° (0.02 mm.); n_D^{25} 1.4855; d^{25} 1.119, from 5-(2-furyl)pentanol and acetylenedicarboxylic ester by method C; **dianilide,** m.p. 99–101°. The **dicarboxyfurylpentyl acetate,** m.p. 102–103°.[505, 529, 530, 511] Chromic acid attacks the side chain with formation of 2-δ-carboxybutyl-3,4-furandicarboxylic acid.[530] Hydrogenation of the ethyl ester over Raney pickel produces 5-(3,4-dicarbethoxy-2-tetrahydrofuryl)-1-pentanol, b.p. 175–180° (0.02 mm.), d^{21} 1.102; n_D^{24} 1.4660.[530]

2-(Carboxyalkyl)-3,4-furandicarboxylic acids

2-Carboxymethyl-3,4-furandicarboxylic acid (3,4-dicarboxy-2-furylacetic acid)



m.p. 205–206°; by condensation of bromopyruvic ester with sodio-β-ketoglutaric ester according to method B. **Trimethyl ester,** m.p. 66°, b.p. 133–135° (0.4 mm.); **triethyl ester,** b.p. 141–145° (0.5 mm.). Hydrogenation of the methyl ester over Raney nickel produced methyl 3,4-dicarbomethoxy-2-tetrahydrofurylacetate, b.p. 140–142.5° (0.2 mm.), which gave a product, m.p. 212–214°, analyzing as a trihydrazide, on treatment with hydrazine.[502]

2-δ-Carboxybutyl-3,4-furandicarboxylic acid [5-(3,4-dicarboxy-2-furyl)valeric acid]:  m.p. 188–190°, 192–193°. Prepared by method C from 5-(2-furyl)valeric acid and ethyl acetylenedicarboxylate,[504, 531, 530] and by method B from bromopyruvic ester and sodio-β-ketosuberic ester.[502] The **triethyl ester,** b.p. 165–166° (0.2 mm.), n_D^{24} 1.4741, d^{24} 1.124, was hydrogenated over nickel-kieselguhr to the corresponding tetrahydrofuran derivative, b.p. 162–168° (0.01 mm.), d^{23} 1.094, n_D^{24} 1.4579. The **3,4-dicarbethoxyfurylvaleryl chloride,** b.p. 177–178° (0.02 mm.), was converted to the corresponding piperidide, b.p. 210–211° (0.02 mm.), d^{24} 1.132; n_D^{24} 1.5006. On hydrolysis with alkali, the latter gave 3,4-dicar-

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[529] Hofmann, *J Am. Chem. Soc.*, **71,** 164 (1949).

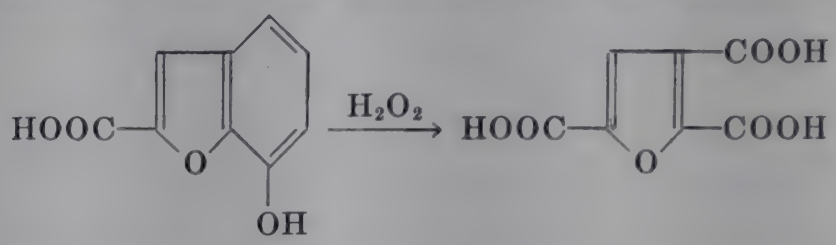
[530] Hofmann, (to Ciba Pharmaceutical Products Inc.), U. S. Patent 2,432,016 (1947); *C. A.*, **42,** 1969 (1948).

[531] Hofmann, (to Ciba Pharmaceutical Products Inc.), U. S. Patent 2,382,418 (1945); *C. A.*, **40,** 365 (1946).

boxyfurylvaleropiperidide, m.p. 132–133°. The **trimethyl ester**, on treatment with ammonia in alcohol, gave rise to a **monoamide**, m.p. 104°, and a **diamide**, m.p. 156–157°.

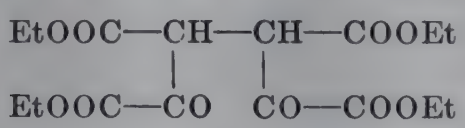
Furanpolycarboxylic Acids

2,3,5-Furantricarboxylic acid was the last of the furanpolycarboxylic acids to be synthesized. It was obtained by oxidation of 7-hydroxy-2-coumaronecarboxylic acid with alkaline hydrogen peroxide.[501] This une-

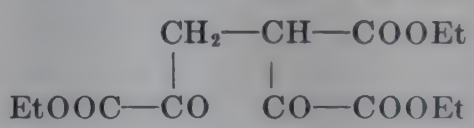


quivocal synthesis was the final proof offered by Reichstein in establishing the structures of the two isomeric tricarboxylic acids of the furan series. A little earlier[82] (see also [331]) he had demonstrated that the product to which Sutter[532] assigned the 2,3,5-configuration was actually 2,3,4-furantricarboxylic acid, but at that time the former was unknown.

Sutter's acid was isolated by the action of hot, dilute hydrochloric acid on the tetracarboxylic ester formed by treatment of the sodiooxaloacetic ester with bromine, and also by similar treatment of the tricarboxylic ester derived from sodiooxaloacetic ester and bromopyruvic ester. He assumed that the intermediate polyesters were formed by C-alkylation (A and B), and quite naturally concluded that the final product was 2,3,5-furantri-

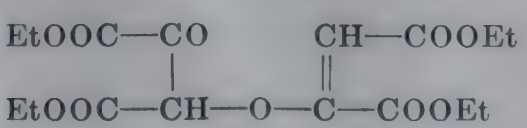


(A)

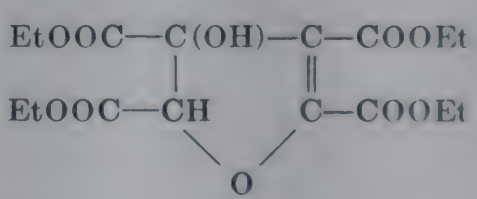


(B)

carboxylic acid. This conclusion was rendered untenable by Reichstein[82] who showed indirectly that the product was the 2,3,4- isomer, and suggested that reaction of ethyl sodiooxaloacetate with bromine proceeds by way of O-alkylation to give C as the intermediate. However, a review of the evidence suggests yet another interpretation[407] in which Sutter's intermediate tetracarboxylic ester is assigned structure D, the formation of which can be visualized by way of the intermediate aldol, E.

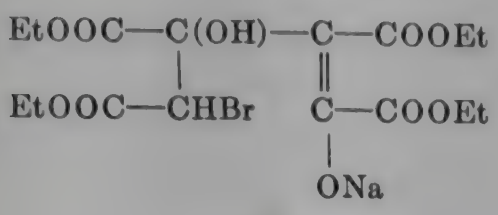


(C)



(D)

[532] Sutter, *Ann.*, **499**, 47 (1932).



(E)

Furan-2,3,5-tricarboxylic acid: trimethyl ester, m.p. 76°, b.p. 130–131° (0.3 mm.). Partial decarboxylation produces 2,4-furandicarboxylic acid[501] (see also [427]).

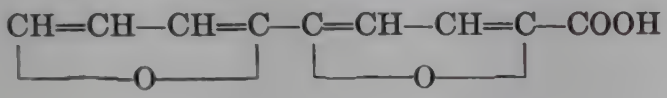
Furan-2,3,4-tricarboxylic acid: m.p. 273° (dec.). **Trimethyl ester,** m.p. 107.5–108.5°; **triethyl ester,** m.p. 37°.[82]

Furan-2,3,4,5-tetracarboxylic acid: m.p. 247° (dec.). **Tetramethyl ester,** m.p. 107–108°, b.p. 175° (0.2 mm.); **tetraethyl ester,** m.p. 34.5°, b.p. 175° (0.2 mm.)[82] (see also [396]). The bacteriostatic properties of the acid were tested by Phatak and Laake.[46]

Carboxylic Acids Related to Bifuryl and Its Homologs

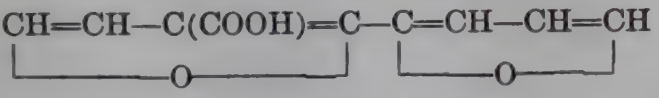
Only a few of the products of this category have been reported, most of which were derived from 2-furoic acid or ester by condensation with aldehydes in concentrated sulfuric acid medium (see p. 506). Several others are mentioned by Brown,[533] but no constants are reported.

5-(2-Furyl)-2-furoic acid (2,2′-bifuryl-5-carboxylic acid)

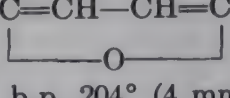


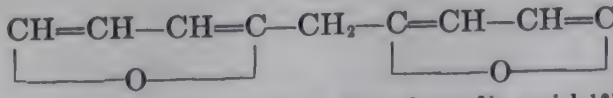
m.p. 154°, by oxidation of the corresponding aldehyde with alkaline silver oxide. Addition to aqueous ferric chloride produces a brown-violet color.[320]

2-(2-Furyl)-3-furoic acid (2,2′-bifuryl-3-carboxylic acid):



m.p. 177–178°, by saponification of the **ethyl ester,** b.p. 142° (7 mm.), obtained by condensation of 2-furoylacetic ester with 1,2-dichloroethyl ethyl ether in aqueous ammonia[411]; or better, in aqueous sodium hydroxide.[320] For a discussion of this, the Benary synthesis, see p. 562.

5-Methylenedi-2-furoic acid:  m.p. 238°, by hydrolysis of the **diethyl ester,** m.p. 39°, b.p. 204° (4 mm.); n_D^{19} 1.5335. The latter obtained as a viscous, pale yellow oil in yield of 4 g. from ethyl 2-furoate (10 g.), and trioxymethylene (1.3 g.) in sulfuric acid at 0° for 0.5 hour.[127] Attempts to prepare the dicarboxylic acid from the corresponding aldehyde by (1) oxidation with alkaline silver oxide, or (2) the oxime → nitrile → acid route, were unsuccessful[320] (see also [130]).

5-Furfuryl-2-furoic acid:  m.p. 118°, by partial decarboxylation of the preceding dicarboxylic acid.[127]

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[533] Brown, *Iowa State Coll. J. Sci.*, **12**, 111 (1937).

5-Ethylidenedi-2-furoic acid: $(HOOC—C=CH—CH=C)_2CHCH_3$; m.p. 216°. **Diethyl ester,** b.p. 210° (5 mm.), n_D^{17} 1.5246; in 6.5 g. yield from ethyl 2-furoate (10 g.), paraldehyde (2.5 cc.) in sulfuric acid at 0°.[127]

5-(1-α-Furylethyl)-2-furoic acid:

$$CH=CH—CH=C—CH(CH_3)—C=CH—CH=C—COOH$$

m.p. 105°; by partial decarboxylation of preceding dicarboxylic acid.[127]

5-Benzylidenedi-2-furoic acid: $(HOOC—C=CH—CH=C—)_2CHC_6H_5$; m.p. 212°, by hydrolysis of the ethyl ester obtained in low yield by condensation of ethyl 2-furoate with benzaldehyde in sulfuric acid.[127]

5-Ethylenedi-2-furoic acid: $\left(HOOC—C=CH—CH=C—CH_2\right)_2$; m.p. 267–269° (dec.), by oxidation of the corresponding dialdehyde.[534] The **dinitrile,** m.p. 115–116°, was prepared by Newth and Wiggins,[379] and converted into the ethyl imidoester (hydrochloride, m.p. 253–255°) which, with ammonia, produced the corresponding amidine (hydrochloride-hydrate, m.p. 251°).

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[534] Fenton and Gostling, *J. Chem. Soc.*, **79,** 807 (1901).

Chapter 13

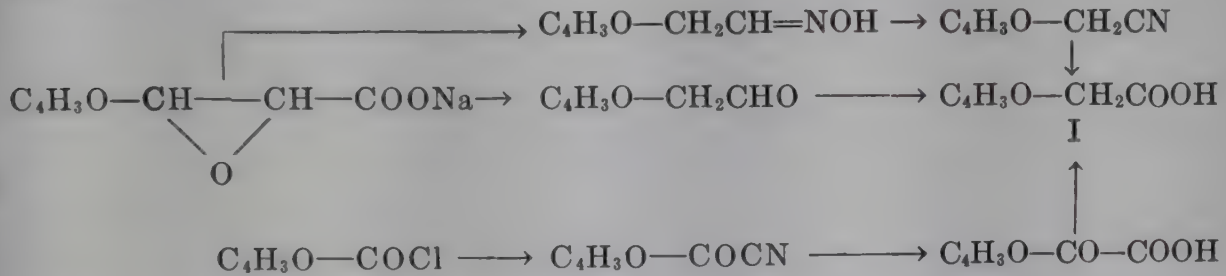
MISCELLANEOUS CARBOXYLIC ACIDS OF THE FURAN SERIES

Furylalkanoic acids

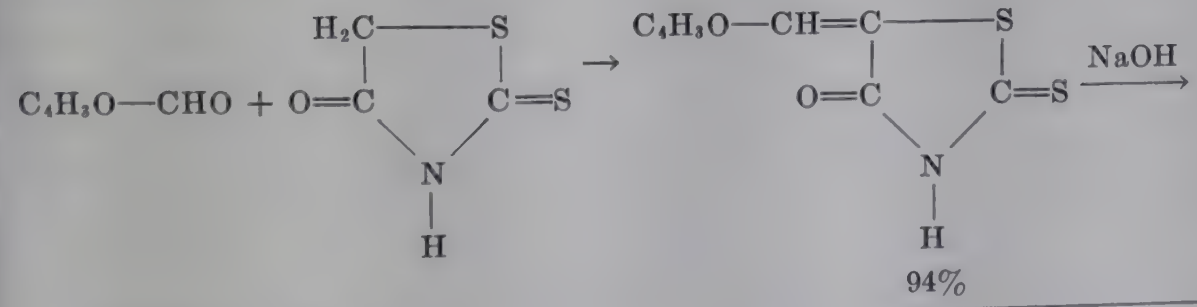
Furylacetic Acids and Their Derivatives

2-Furylacetic acid is a crystalline compound with an odor reminiscent of phenylacetic acid; colorless plates or needles from petroleum ether, m.p. 67–68°; b.p. 102–104° at 0.4 mm. It is soluble in about 15 parts of water at 15°, and is only slightly volatile with steam.[1, 2] At 250–260° the pure acid decomposes with loss of carbon dioxide to give 2-methylfuran in good yield.[3]

Synthesis of the acid, I, has been accomplished by oxidation of the corresponding aldehyde derived from sodium 3-(2-furyl)glycidate, and by saponification of 2-furylacetonitrile.[1] It is also obtained by reduction of 2-furylglyoxylic acid (2-furoylformic acid) using sodium methoxide and hydrazine hydrate.[1, 2]



2-Furylacetic acid is best obtained by the rhodanine method, however, the over-all yield (based on furfural) being in excess of 70 per cent of the theoretical amount[4] (see also [5, 6]). The reactions involved are illustrated below:



[1] Reichstein, *Ber.*, **63**, 749 (1930).
[2] Reichstein and Morsman, *Helv. Chim. Acta*, **17**, 1119 (1934).
[3] Runde, Scott and Johnson, *J Am. Chem. Soc.*, **52**, 1284 (1930).
[4] Plucker and Amstutz, *J. Am. Chem. Soc.*, **62**, 1512 (1940).

$$C_4H_3O—CH_2CS—COOH \xrightarrow{NH_2OH} C_4H_3O—CH_2C(NOH)—COOH \xrightarrow[-CO_2]{Ac_2O}$$

99% 93%

$$C_4H_3O—CH_2CN \xrightarrow{NaOH} C_4H_3O—CH_2COOH$$

88% 96%

The urea derivative of furylacetic acid, $C_4H_3O—CONHCONH_2$ (m.p. 186–187°) was tested as an anticonvulsant, but exhibited little or no activity.[7]

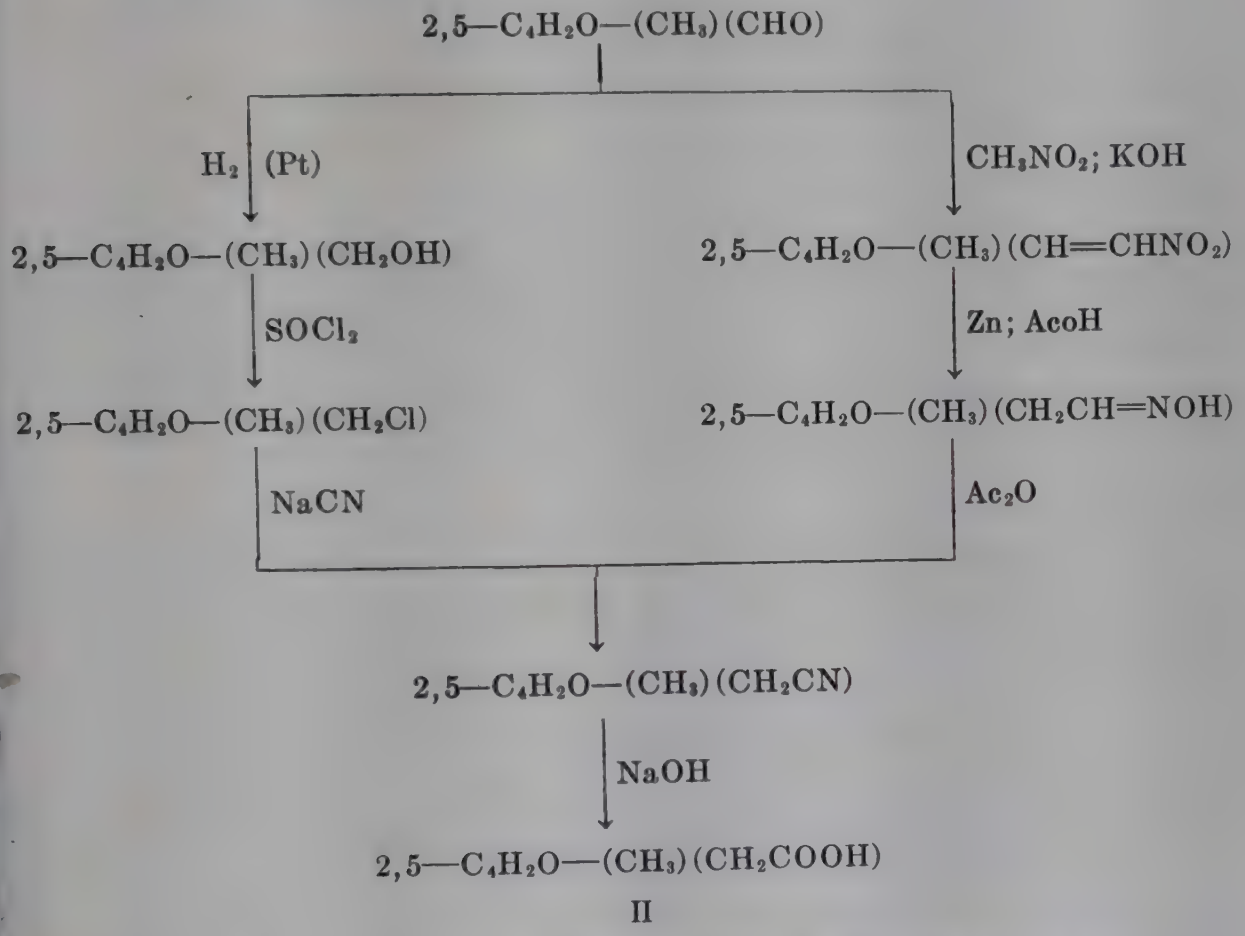
TABLE 1. DERIVATIVES OF 2-FURYLACETIC ACID

Derivative	Physical constants (°C.)	Ref.
Esters		
methyl	b.p. 74–75 (11 mm.), 87–88 (21 mm.) n_D^{25} 1.4638; d_4^{25} 1.1250	2, 8
ethyl	b.p. 82.2 (9 mm.), 88 (15 mm.) n_D^{25} 1.4571; d_4^{25} 1.0763	6, 8
n-propyl	b.p. 115–116 (34 mm.) n_D^{25} 1.4558; d_4^{25} 1.0436	8
i-propyl	b.p. 92–93 (17 mm.) n_D^{25} 1.4511; d_4^{25} 1.0338	8
n-butyl	b.p. 110–111 (13 mm.) n_D^{25} 1.4558; d_4^{25} 1.0232	8
i-butyl	b.p. 112–113 (21 mm.) n_D^{25} 1.4518; d_4^{25} 1.0168	8
Acid chloride	b.p. 65 (1 mm.)	1
Amido derivatives		
N-2-hydroxyethyl	oil	9
N-phenyl	m.p. 84–85	1
N-2,5-diethoxyphenyl	—	10

3-Furylacetic acid: 3-$C_4H_3O—CH_2COOH$; m.p. 61.9–62.2°; **acid chloride,** b.p. *ca.* 53° (3 mm.); **amide,** m.p. 114–115°; **anilide,** m.p. 122.6–123.2°.[11]

[5] Gränacher, *Helv. Chim. Acta*, **5**, 610 (1922).
[6] Hinz, Meyer and Schücking, *Ber.*, **76**, 676 (1943).
[7] Spielman, Geiszler and Close, *J. Am. Chem. Soc.*, **70**, 4189 (1948).
[8] Ryan, Plucker and Amstutz, *J. Am. Chem. Soc.*, **62**, 2037 (1940).
[9] Jones, Soper, Behrens and Corse, *J Am. Chem. Soc.*, **70**, 2843 (1948).
[10] Lense, Glover and Markham, *Virginia J. Sci.*, **3**, 31 (1942); *C. A.*, **36**, 3114 (1942).
[11] Sherman and Amstutz, *J. Am. Chem. Soc.*, **72**, 2195 (1950).

5-Methyl-2-furylacetic acid, II (m.p. 61–62°), has been synthesized by condensation of 5-methylfurfural with nitromethane, followed by reduction to the oxime, dehydration to the nitrile, and finally, hydrolysis.[12] Alternatively, the aldehyde may be reduced to the corresponding alcohol and converted to the acid by way of 5-methylfurfuryl chloride and the nitrile.[12] Wolff-Kizhner reduction of 5-methyl-2-furylglyoxylic acid likewise gives rise to II,[13] and more recently it has been reported, as a by-product, following carbonation of the Grignard complex derived from 3-hexen-5-yn-2-ol.[14]



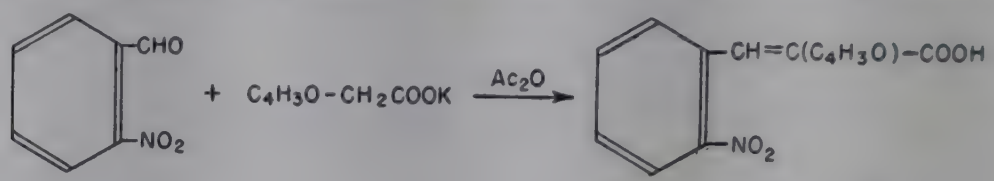
Inasmuch as 2-furylacetic esters possess a reactive alpha-methylene group, they can undergo the condensation reactions common to such types. For example, they react with acetic and oxalic esters, under the influence of sodium or sodium ethoxide, to give the expected keto esters, α-(2-furyl)-acetoacetic ester and α-(2-furyl)oxaloacetic ester, respectively[6] (see also [2]). Similarly, condensation with ethyl formate gives rise to α-(2-furyl)formyl-acetic ester, III.

$$C_4H_3O—CH_2COOR + HCOOR \xrightarrow{-ROH} \underset{III}{C_4H_3O—CH(CHO)—COOR}$$

[12] Scott and Johnson, *J Am. Chem. Soc.*, **54**, 2549 (1932).
[13] Reichstein and Zschokke, *Helv. Chim. Acta*, **15**, 249 (1932).
[14] Haynes and Jones, *J. Chem. Soc.*, **1946**, 503.

Ethyl α-(2-furyl)formylacetate: III (R = C_2H_5); b.p. 105–107° (9.5 mm.); in 71 per cent yield by the method illustrated above. The ester is an oily liquid which discolors rapidly on standing. With phenylhydrazine it is converted into a viscous, non-crystallizing product.[6]

The Perkin reaction of 2-furylacetic acid with *o*-nitrobenzaldehyde, yields a mixture of *cis*- and *trans*-α-(2-furyl)-*o*-nitrocinnamic acid, IV.[15] The related furfurylidenefurylacetic ester (2,3-difurylacrylic ester) is reported as the product of the Claisen condensation of furfural with furylacetic



IV

ester, but no physical constants are given.[16]

α-(2-Furyl)-*o*-nitrocinnamic acid (*o*-nitrobenzylidenefurylacetic acid); IV; *cis* form, m.p. 192–192.4°; *trans* form, m.p. 137.6–138.2°. Reduction of the *trans*-isomer using ammoniacal ferrous sulfate yielded the corresponding amino derivative, m.p. 156°, which failed to undergo Pschorr ring closure. Decarboxylation gave *cis*- and *trans*-*o*-nitrophenyl-2-furylethylene, respectively.[15]

Furylpropionic Acids

2-(2-Furyl)propionic acid, 2-(C_4H_3O)—$CH(CH_3)$—COOH, the furan analog of hydratropic acid, has not been described. However, the 3-(2-furyl) substituted acid and a number of related acids are known.

3-(2-Furyl)propionic acid, I (m.p. 56.6–57.6°, 58–59°), was first isolated by Baeyer who reduced 3-(2-furyl)acrylic acid with sodium amalgam[17] (see also [18, 19]). It is also produced by decarboxylation of furfurylmalonic acid[20] or 2-furylsuccinic acid[21]; by hydrolytic fission of furfurylacetoacetic ester using very concentrated alkali[22]; by oxidation of 3-(2-furyl)propionaldehyde[23]; and by the action of carbon dioxide on 2-(2-furyl)ethylmagnesium chloride.[24]

$$C_4H_3O—CH_2CH_2Cl \xrightarrow{Mg} C_4H_3O—CH_2CH_2MgCl \xrightarrow{CO_2} C_4H_3O—CH_2COOH$$

I

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[15] Amstutz and Spitzmiller, *J. Am. Chem. Soc.*, **65**, 367 (1943).

[16] Rothrock (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,381,884 (1945); *C. A.*, **39**, 5126 (1945).

[17] Baeyer, *Ber.*, **10**, 355 (1877).

[18] Marckwald, *Ber.*, **20**, 2811 (1887).

[19] Sudborough and Gittins, *J. Chem. Soc.*, **95**, 315 (1909).

[20] Marckwald, *Ber.*, **21**, 1080 (1888).

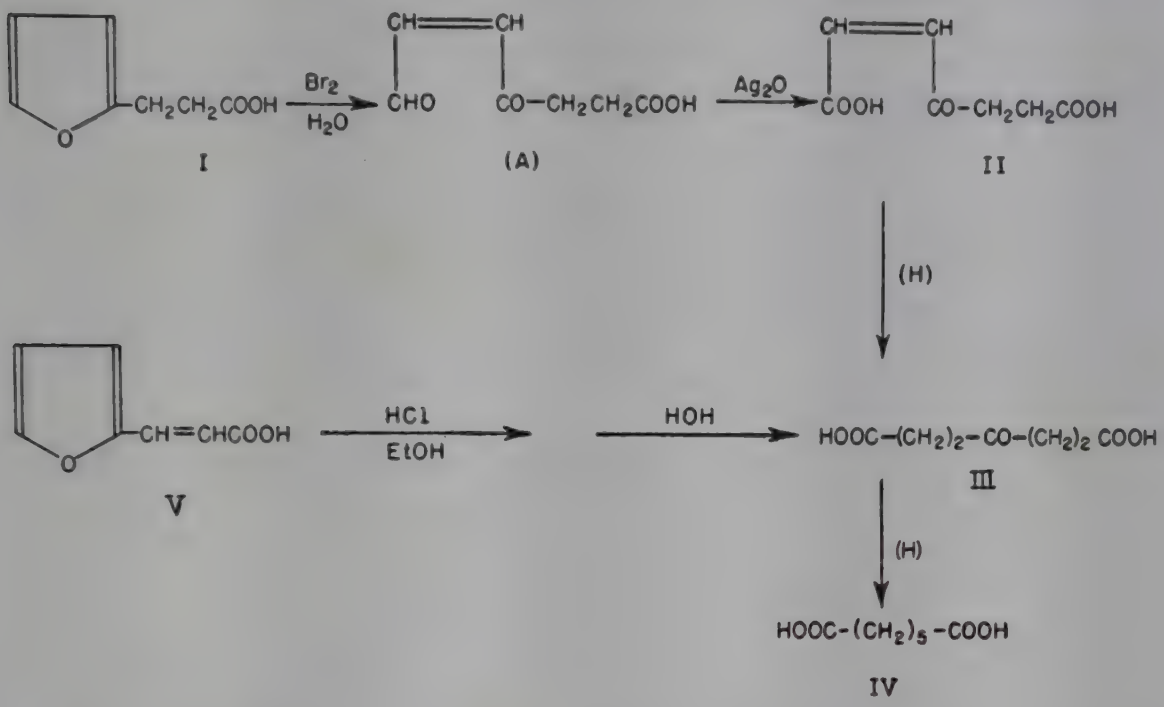
[21] Sandelin, *Ber.*, **31**, 1119 (1898).

[22] Kirner and Richter, *J. Am. Chem. Soc.*, **51**, 3131 (1929).

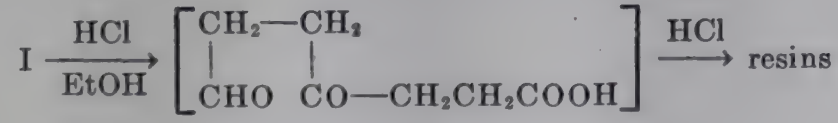
[23] Sherlin, Berlin, Serebrennikova and Rabinovich, *J. Gen. Chem. U.S.S.R.*, **8**, 7 (1938); *C. A.*, **32**, 5397 (1938).

[24] Amstutz and Plucker, *J. Am. Chem. Soc.*, **63**, 206 (1941).

Oxidation of I with aqueous bromine leads to rupture of the nucleus with the formation of A, which on treatment with silver oxide gives rise to 4-oxo-2-heptene-1,7-dioic acid, II, which Baeyer[25] (see also [26, 27]) named "furonic" acid. Subsequently, Baeyer[28] reduced II to ketopimelic acid, III, and finally to pimelic acid IV. III may also be obtained directly from



3-(2-furyl)acrylic acid, V, by the action of alcoholic hydrochloric acid (p. 652), whereas similar treatment of I gives resinous products due, no doubt, to the reactivity of the probable hydrolysis product, VI. On the other hand, 5-substituted homologs of I on treatment with hydrochloric acid are converted into more stable 1,4-diketone types (discussion to follow) (see also p. 641) which have been isolated in good yield in a number of instances.



VI

Catalytic hydrogenation of 3-(2-furyl)propionic acid over a palladium catalyst gives the saturated acid, 3-(tetrahydro-2-furyl)propionic acid, b.p. 157° at 18 mm.; d_4^{19} 1.1272; n_D^{19} 1.462.[23]

For the activity of furylpropionic acid as a plant growth promoter, see

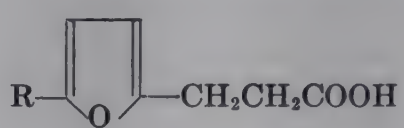
[25] Baeyer, *Ber.*, **10**, 696 (1877).
[26] Fujita, *J. Pharm. Soc. Japan*, **493**, 148 (1923); *C. A.*, **17**, 3030 (1923).
[27] Carter, *J. Am. Chem. Soc.*, **50**, 2299 (1928).
[28] Baeyer, *Ber.*, **10**, 1358 (1877).

Tamari.[29] The bacteriostatic properties were tested by Feasley *et al.*[30] For condensations with thiourea, see Andrisano.[31]

Derivatives of 3-(2-furyl)propionic acid: **methyl ester,** b.p. 89° (15 mm.), d_4^{20} 1.088, n_D^{20} 1.4662[25]; **ethyl ester,** b.p. 101–102° (22 mm.), d_4^{25} 1.0527[32]; **piperidide,** b.p. 153–154° (1 mm.)[33]; **amide,** m.p. 98°[18]; **homopiperonylamide,** m.p. 92°[34]; ***N*-[3-(2-furyl) propionyl]glycine,** 2-C_4H_3O—$CH_2CH_2CONHCH_2COOH$, m.p. 118°.[35]

2,5-Furandipropionic acid: $HOOC(CH_2)_2$—C_4H_2O—$(CH_2)_2COOH$; m.p. 151–152°, 154–154.5°, by reduction of 2,5-furandiacrylic acid with sodium amalgam[36] and also by oxidation of 2,5-furandipropionaldehyde.[23] **Dimethyl ester,** m.p. 56.5–57.5°, b.p. 172–174° (12 mm.). On heating the acid in alcoholic hydrochloride for six hours, Cooper and Nuttall[36] noted no effect, whereas on boiling with concentrated HCl, Sherlin[23] (see also Chaper 14) reports fission of the furan nucleus and formation of 3,6-dioxoöctane-1,8-dicarboxylic acid, $(—CH_2COCH_2CH_2COOH)_2$ (*note:* Erdmann[37] proposed a synthesis of the acid by ring closure of the latter, but did not attempt it experimentally). Aqueous bromine attacks the acid readily, giving an acidic product(s) containing bromine.[36]

Nuclear substituted 3-(2-furyl)propionic acids of the type



(where R = alkyl or aryl)[a] may be obtained by reduction of the corresponding substituted acrylic acids.[38] They can also be synthesized from the appropriate saturated 1,4-diketo compounds. For example, 3-(5-methyl-2-furyl)propionic acid, VII, is formed in 50 per cent yield by refluxing 4,7-dioxoöctanoic acid (acetonyllevulinic acid), VIII[b] in benzene in the presence of phosphorus pentoxide.[39] Actually esterification of VIII using an acid catalyst, brings about "furanization" to a considerable degree; a mixture of the esters of VII and VIII is formed.[38] Esterification of VII, in like manner, also gives rise to both products, the relative proportions varying with the concentration of acid catalyst.[39] The reactions involved are

[a] No products of this general type are known wherein R is located at other than the 5-nuclear position.

[b] For the formation of VIII and the related phenacyllevulinic acid by cleavage-rearrangement of furfurylideneacetone and furfurylideneacetophenone, respectively, see Chapter 14.

[29] Tamari, *J. Agr. Chem. Soc. Japan*, **17**, 321 (1941); *C. A.*, **41**, 4545 (1947).

[30] Feasley, Gwynn, Degering and Tetrault, *J. Am. Pharm. Assoc.*, **30**, 41 (1941).

[31] Andrisano, *Boll. sci. facoltà chim. ind. univ. Bologna*, **5**, 42, 45, 48 (1944–1947); *C. A.*, **44**, 3904 (1950).

[32] Hughes and Johnson, *J. Am. Chem. Soc.*, **53**, 737 (1931).

[33] Asano and Nakatomi, *J. Pharm. Soc. Japan*, **53**, 176 (1933); *C. A.*, **27**, 2703 (1933).

[34] Raman, *J. Indian Chem. Soc.*, **17**, 715 (1940); *C. A.*, **35**, 6593 (1941).

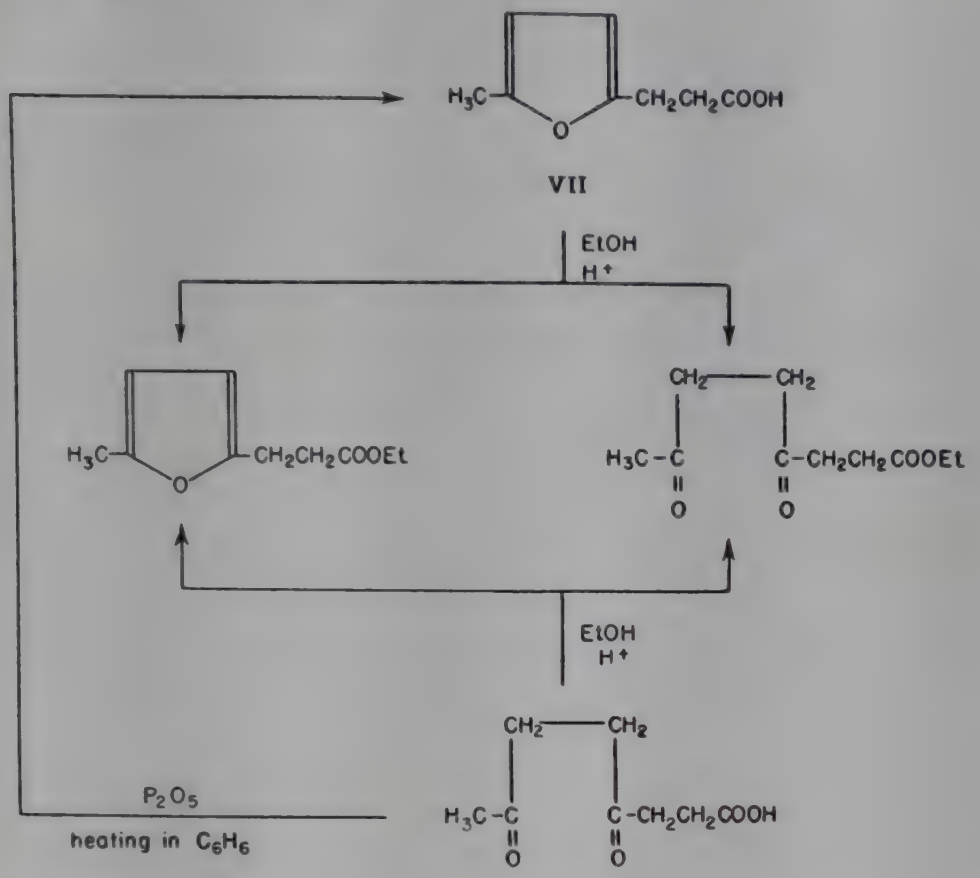
[35] Sasaki, *Biochem. Z.*, **25**, 272 (1910); *C. A.*, **4**, 2004 (1910).

[36] Cooper and Nuttall, *J. Chem. Soc.*, **105**, 2218 (1914).

[37] Erdmann, *Ber.*, **24**, 3201 (1891).

[38] Wichterle, *Collection Czech. Chem. Commun.*, **11**, 171 (1939); *C. A.*, **33**, 6301 (1939).

illustrated below for the methyl substituted acid. 4,7-Dioxo-7-phenylheptanoic acid (ω-phenacyllevulinic acid) behaves similarly to VIII, giving 3-(5-phenyl-2-furyl)propionic acid when heated in the presence of a suitable dehydrating agent[39] (see also [40, 41]).



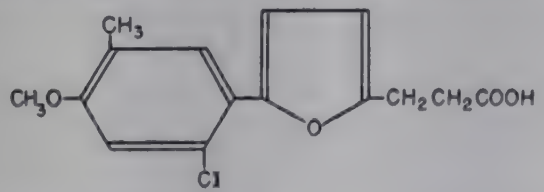
VIII

3-(5-Methyl-2-furyl)propionic acid: The constants reported in the literature are not in good agreement: m.p. 54–55°,[39] 61–62°[38]; **methyl ester** b.p. 83° (2–3 mm.)[39]; **ethyl ester,** b.p. 136° (2–3 mm.)[39]; 102–102.5° (9.5 mm.)[38]; **amide,** m.p. 99–100°.[38]

3-(5-Phenyl-2-furyl)propionic acid: m.p. 113–115, 116°; **ethyl ester,** m.p. 20–21°, b.p. 165–167° (2–3 mm.), n_D^{28} 1.5508; **hydrazide,** m.p. 110°[39] (see also[40]). The ethyl ester with homopiperonylamine gives the corresponding amido derivative, m.p. 104–105°.[34]

3-(5-*p*-Methoxyphenyl-2-furyl)propionic acid: m.p. 141°; **ethyl ester,** m.p. 52°, b.p. 189–195° (2 mm.); **hydrazide,** m.p. 136°.[39]

3-[5-(3-Methyl-4-methoxy-6-chlorophenyl)-2-furyl]propionic acid:



m.p. 175–177°; **methyl ester,** m.p. 77–78°.[42]

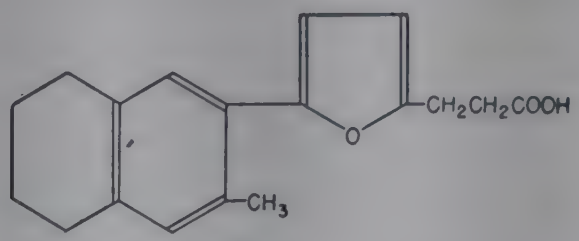
[39] Robinson and Todd, *J. Chem. Soc.*, **1939,** 1743.

[40] Blicke, Warzynski, Faust and Gearien, *J. Am. Chem. Soc.*, **66,** 1675 (1944).

[41] Butenandt, Dannenberg and Dresler, *Z. Naturforsch.*, **4,** b, 69 (1949); *C. A.*, **44,** 3966 (1950).

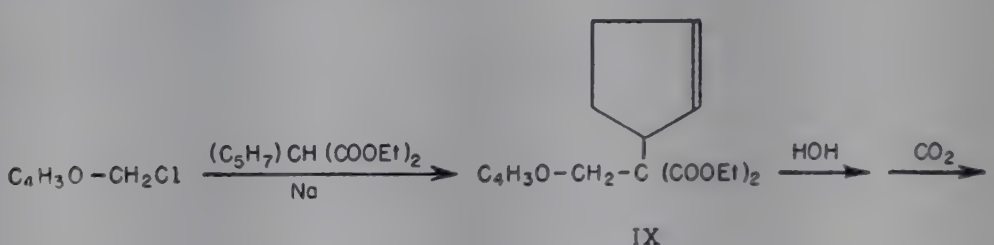
[42] Martin and Robinson, *J. Chem. Soc.*, **1943,** 497.

3-[5-(3-Methyl-5,6,7,8-tetrahydro-2-naphthyl)-2-furyl] propionic acid: m.p. 143°.[41]

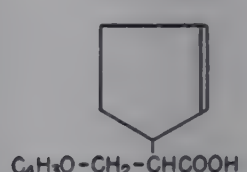


The following 3-(2-furyl)propionic acids possess one or more substituent groups in the side chain.

3-(2-Furyl)-2-(2-cyclopentenyl)propionic acid: X (below); b.p. 110° (0.07 mm.), d_4^{25} 1.1239; n_D^{25} 1.5090. Prepared by hydrolysis and decarboxylation of furfurylcyclopentenylmalonic ester, IX, derived from cyclopentenylmalonic ester and furfuryl chloride under the influence of sodium. The **β-diethylaminoethyl ester,** m.p. 69–78°, was tested as an antispasmodic agent.[43]



IX



X

3-(2-Furyl)-2-cyclopentylpropionic acid: b.p. 105° (0.025 mm.), d_4^{25} 1.1010; n_D^{25} 1.4962; by reduction of IX, saponification and decarboxylation. **β-Diethylaminoethyl ester,** m.p. 81–88°.[43]

3-(2-Furyl)-2-(2-cyclohexenyl)propionic acid: b.p. 111° (0.03 mm.), d_4^{25} 1.1153; n_D^{25} 1.5140; from furfuryl chloride and cyclohexenylmalonic ester by the step outlined above.[43]

3-(2-Furyl)-3-phenylpropionic acid: $C_4H_3O—CH(C_6H_5)CH_2COOH$; m.p. 105°, b.p. 186° (15 mm.), by the action of PhMgBr on N-disubstituted 3-(2-furyl)acrylamides and subsequent hydrolysis[44]; also by decarboxylation of 2-(2-furyl)-2-phenyl-1,1-ethanedicarboxylic acid, $C_4H_3O—CH(C_6H_5)—CH(COOH)_2$.[45] **Ethyl ester,** b.p. 172° (15 mm.); **acid chloride,** b.p. 88° (31 mm.); **amide,** m.p. 137.5°; **substituted amides:** N-diethyl, b.p. 218° (38 mm.); N-diphenyl, m.p. 83°, b.p. 291° (12 mm.); N-methyl-N-phenyl, b.p. 213° (11 mm.); N-ethyl-N-phenyl, b.p. 236° (14 mm.).

3-(2-Furyl)-2,3-diphenylpropionic acid: $C_4H_3O—CH(C_6H_5)—CH(C_6H_5)—COOH$; m.p. 172°; obtained via the appropriate derivatives by the action of PhMgBr on

[43] Moffett, Hart and Hoehn, *J. Am. Chem. Soc.*, **69**, 1849 (1947).
[44] Maxim and Zugravescu, *Bull. soc. chim.* (5), **1**, 1087 (1934).
[45] Maxim and Georgescu, *Bull. soc. chim.* (5), **3**, 1114 (1936).

3-(2-furyl)-2-phenylacrylic ester,* N-disubstituted amides or the nitrile.[46, 47] **Esters:** ethyl, b.p. 210° (8 mm.); propyl, b.p. 226° (9 mm.); butyl, b.p. 230° (9 mm.); pentyl, b.p. 236° (9 mm.); **acid chloride,** b.p. 210° (4 mm.); **amide,** m.p. 179°; **substituted amide:** N-methyl-N-phenyl, b.p. 262° (13 mm.); **nitrile,** b.p. 225° (15 mm.).

* In this case, 3-furyl-1,1,2-triphenyl-2-propene-1-ol

$$[C_4H_3O{-}CH{=}C(C_6H_5){-}C(C_6H_5)_2OH]$$

is also obtained (see also [48]).

3-(2-Furyl)-3-(*p*-tolyl)-2-phenylpropionic acid:

$$C_4H_3O{-}CH(C_6H_4{-}p{-}CH_3){-}CH(C_6H_5){-}COOH$$

m.p. 163°; by saponification of the **nitrile** (b.p. 219° (20 mm.)) obtained by the action of *p*-tolylmagnesium bromide on 3-(2-furyl)-2-phenylacrylonitrile.[49]

Furylbutyric Acids

Two of the simple furylbutyric acids have been described, the 2-(2-furyl) and 4-(2-furyl) isomers. The former, I (m.p. 50°; amide, m.p. 96–98°, b.p. 150–152° (12 mm.)), was obtained by ethylation of 2-furylmalonic ester, hydrolysis and decarboxylation.[2]

$$C_4H_3O{-}CH(COOR)_2 \xrightarrow[NaOMe]{C_2H_5I} C_4H_3O{-}C(C_2H_5)(COOR)_2 \xrightarrow{HOH} \xrightarrow{-CO_2} C_4H_3O{-}CH(C_2H_5)COOH \quad (I)$$

4-(2-Furyl)butyric acid, II (b.p. 94–117° (0.03 mm.)); anilide, m.p. 62–64°), was derived from 3-(2-furyl)-1-propanol. Conversion of the latter to the chloride, treatment with potassium cyanide and subsequent hydrolysis produced the acid. The ethyl ester (b.p. 119–122° (23 mm.)) is easily reduced by sodium amalgam to 4-(2-furyl)-1-butanol.[50, 51]

$$C_4H_3O{-}(CH_2)_3OH \xrightarrow{SOCl_2} \xrightarrow{KCN} \xrightarrow{KOH} C_4H_3O{-}(CH_2)_3COOH \quad (II)$$

The substituted furylbutyric acids (III) described below were obtained, via the corresponding nitriles, by the action of methylmagnesium iodide and benzylmagnesium chloride, respectively, on 3-(2-furyl)-2-phenylacrylonitrile.[49]

$$C_4H_3O{-}CH{=}C(C_6H_5)CN \xrightarrow{RMgX} \xrightarrow{NaOH} C_4H_3O{-}CHR{-}CH(C_6H_5)COOH \quad (III)$$

[46] Maxim and Stancovici, *Bull. soc. chim.* (*5*), **3**, 1319 (1936).
[47] Maxim and Aldea, *Bull. soc. chim.* (*5*), **2**, 582 (1935).
[48] Maxim and Georgescu, *Bull. soc. chim.* (*5*), **3**, 2226 (1936).
[49] Maxim and Aldea, *Bull. soc. chim.* (*5*), **3**, 1329 (1936).
[50] Hofmann, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **71**, 1253 (1949).
[51] Hofmann (to Ciba Pharmaceutical Products Inc.), U. S. Pat. 2,527,421 (1950).

3-(2-Furyl)-2-phenylbutyric acid: III (R = CH_3); b.p. 208° (18 mm.). **Ethyl ester,** b.p. 128° (15 mm.); **acid chloride,** b.p. 165° (12 mm.); **amide,** b.p. 221° (15 mm.); **nitrile,** b.p. 167° (10 mm.).
3-(2-Furyl)-2,4-diphenylbutyric acid: III (R = $C_6H_5CH_2$); m.p. 118°. **Ethyl ester,** b.p. 230° (17 mm.); **acid chloride,** b.p. 184° (17 mm.); **amide,** m.p. 165°; **nitrile,** b.p. 241° (18 mm.).

Furylvaleric Acids

5-(2-Furyl)valeric acid: II (below); m.p. 42–43°, by the sequence of steps indicated below.[52, 53, 54, 51]

$$C_4H_3O{-}CH{=}CH{-}CHO \xrightarrow{CH_2(COOH)_2}$$

$$C_4H_3O{-}CH{=}CH{-}CH{=}C(COOH)_2 \xrightarrow{H_2(Pd)} \xrightarrow{-CO_2}$$

I

$$C_4H_3O{-}(CH_2)_4{-}COOH$$

II

Hofmann[52] was unable to duplicate the earlier modified synthesis employed by Asano and Nakatomi[33] in which 4-(2-furyl)-1,3-butadiene-1,1-dicarboxylic acid, I, was decarboxylated prior to reduction. Derivatives of II: **ethyl ester,** b.p. 130–133° (16 mm.); **anilide,** m.p. 75–76°; **piperidide,** b.p. 175–176° (3 mm.).
2-(Furfuryl)butyric acid [3-(2-furyl)-2-ethylpropionic acid]:

$$C_4H_3O{-}CH_2CH(C_2H_5){-}COOH$$

b.p. 174–176° (46 mm.). Prepared by reduction of 3-(2-furyl)-2-ethylacrylic acid (furylangelic acid) with sodium amalgam.[27] It was earlier obtained by Tonnies[55] who incorrectly assigned to it the structure of 5-(2-furyl)valeric acid based on Baeyer's[56] misconception of the structure of furylangelic acid. Oxidation in two steps with aqueous bromine and silver oxide, followed by reduction using hydriodic acid and red phosphorus, yields 2-ethylpimelic acid,[27] and not azelaic acid as originally reported by Tonnies.[55]
3-(2-Furyl)valeric acid: $CH_3CH_2CH(C_4H_3O){-}CH_2COOH$; b.p. 145° (17 mm.), by the action of EtMgBr on 3-(2-furyl)acryl-N-diphenylamide and subsequent saponification. **Amido derivatives:** N-diethyl, b.p. 196° (41 mm.); N-diphenyl, b.p. 253° (15 mm.); N-methyl-N-phenyl, b.p. 130° (3 mm.); N-ethyl-N-phenyl, b.p. 211° (27 mm.).[44]
3-(2-Furyl)-2-phenylvaleric acid: $CH_3CH_2CH(C_4H_3O){-}CH(C_6H_5){-}COOH$; m.p. 93°, obtained via the appropriate derivatives, by the action of EtMgBr on 3-(2-furyl)-2-phenylacrylic ester, disubstituted amide or nitrile.[47, 46] **Esters:** ethyl, b.p. 158° (9 mm.), 180° (22 mm.); propyl, b.p. 170° (8 mm.); butyl, b.p. 179° (10 mm.); pentyl, b.p. 192° (7 mm.); **acid chloride,** b.p. 167° (18 mm.); **amide,** m.p. 136°; **substituted amides:** N-diethyl, b.p. 223° (12 mm.); N-diphenyl, b.p. 262° (11 mm.); N-methyl-N-phenyl, b.p. 244° (12 mm.); **nitrile,** b.p. 181° (18 mm.).

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[52] Hofmann, *J. Am. Chem. Soc.*, **66**, 51 (1944).
[53] Hofmann (to Ciba Pharmaceutical Products Inc.) U. S. Pat. 2,432,016 (1947); *C. A.*, **42**, 1969 (1948).
[54] Hofmann, *J. Am. Chem. Soc.*, **67**, 421 (1945).
[55] Tonnies, *Ber.*, **12**, 1200 (1879).
[56] Baeyer and Tonnies, *Ber.*, **10**, 1364 (1877).

Higher Furylalkanoic Acids

3-(2-Furyl)caproic acid: $CH_3(CH_2)_2CH(C_4H_3O)—CH_2COOH$; b.p. 148° (11 mm.), 152° (15 mm.). Prepared by saponification of the product obtained by treatment of 3-(2-furyl)acryl-N-diphenylamide with PrMgBr.[44] Also by the action of this Grignard reagent on furfurylidenecyanoacetic ester, followed by saponification to the dicarboxylic acid and subsequent decarboxylation.[45] **N-diphenylamide,** b.p. 241° (10 mm.).

3-(2-Furyl)-5-methylcaproic acid: $CH_3CH(CH_3)CH_2CH(C_4H_3O)—CH_2COOH$; b.p. 153° (15 mm.), obtained by treatment of furfurylidenecyanoacetic ester or furfurylidenemalonic ester with *i*-BuMgBr, saponification to the dicarboxylic acid and, finally, decarboxylation.[45]

3-(2-Furyl)-6-methylheptanoic acid:

$$CH_3CH(CH_3)—(CH_2)_2—CH(C_4H_3O)—CH_2COOH$$

b.p. 156° (8 mm.), by the action of *i*-$C_5H_{11}MgBr$ on furfurylidenemalonic ester, saponification and decarboxylation.[45]

3-(2-Furyl)-2-phenylcaproic acid: $CH_3—(CH_2)_2—CH(C_4H_2O)—CH(C_6H_5)—COOH$; m.p. 124°, from the corresponding nitrile derived from 3-(2-furyl)-2-phenylacrylonitrile and PrMgBr. **Ethyl ester,** b.p. 184° (18 mm.); **acid chloride,** b.p. 174–175° (18 mm.) **amide,** m.p. 164°; **nitrile,** b.p. 191° (23 mm.).[47]

3-(2-Furyl)-2-phenyl-5-methylcaproic acid:

$$CH_3CH(CH_3)CH_2CH(C_4H_3O)—CH(C_6H_5)—COOH$$

m.p. 107°. Same preparation as above, using *i*-BuMgBr. **Ethyl ester,** b.p. 184–185° (18 mm.); **acid chloride,** 185° (25 mm.); **amide,** m.p. 132°; **nitrile,** b.p. 187° (19 mm.).[47]

3-(2-Furyl)-2-phenyl-6-methylheptanoic acid:

$$(CH_3)_2CH—(CH_2)_2—CH(C_4H_3O)—CH(C_6H_5)—COOH$$

b.p. 215° (12 mm.). Prepared as above, using *i*-$C_5H_{11}MgBr$. **Ethyl ester,** b.p. 192° (20 mm.); **acid chloride,** b.p. 187° (10 mm.); **amide,** m.p. 130°; **nitrile,** b.p. 187° (13 mm.).[49]

Furylalkanoic Acids with Additional Functional Group in Side Chain

Hydroxy Acids and Related Compounds

Furylglycollic acid, the furan analog of mandelic acid, has only recently been described by Normant[57] who prepared it from furfural cyanohydrin benzoate (see also [58]). Earlier, it had been reported in 59 per cent yield by reduction of furoylformic acid with sodium amalgam[59] and, as the ethyl ester, by treatment of furfural cyanohydrin with aqueous-alcoholic hydrogen chloride,[60] but no constants were given in these instances.

[57] Normant, *Compt. rend.*, **225,** 580 (1947).

[58] Lukeš, Kastner, Gut and Herben, *Collection Czechoslov. Chem. Communs.*, **12,** 647 (1947); *C. A.*, **42,** 5852 (1948).

[59] Fischer and Brauns, *Ber.*, **46,** 892 (1913).

[60] Matheson and Blaikie, Brit. Pat. 264,143 (1926); *C. A.*, **22,** 91 (1928).

$$C_4H_3O{-}CH(OCOC_6H_5){-}CN \xrightarrow[EtOH - Et_2O]{HCl(g.)} C_4H_3O{-}CH(OCOC_6H_5){-}COOEt \xrightarrow{KOH} C_4H_3O{-}CHOH{-}COOH$$

Dextro-rotatory β-furyllactic acid has been obtained from D,L-furylalanine by a bacterial procedure.[61] Reformatsky[62] indicates that furfural condenses with α-bromo-*i*-butyric acid under the influence of zinc to give the expected β-hydroxy acid in 62 per cent yield, but does not describe the product. Other hydroxy acids containing the furan nucleus were prepared by treating the appropriate keto ester with the Grignard reagent.[63]

Furylglycollic acid (furyl-hydroxyacetic acid); $C_4H_3O{-}CHOH{-}COOH$; m.p. 117° (dec.). Decomposes in the cold on treatment with $SOCl_2$; at higher temperatures by the action of acid chlorides, HCl, $ZnCl_2$ and SeO_2. **Salts:** K, m.p. 151–152°; Na, m.p. 144°; $PhCH_2NH_2$, m.p. 141–142° (dec.); $PhNHNH_2$, m.p. 62–63°; cinchonine, m.p. 166–167°. For the trypanocidal activity of the sodium salt, see Ziering and Buck.[64] **Esters:** methyl, b.p. 115–116° (15 mm.), d_{16}^{8} 1.263; ethyl, b.p. 113–114° (11 mm.); phenacyl, m.p. 96–97°; benzyl, m.p. 50–51°. The sodium salt in ethanol was hydrogenated over Raney nickel to tetrahydrofurylglycollic acid, m.p. 129°.[57] $C_4H_3O{-}CH(OBz){-}COOR$, where R = CH_3, m.p. 103°; where R = C_2H_5, m.p. 120.[58] The following derivatives (I and II) were prepared by Ridi[65] by condensation of furfural with benzonitrile and its derivatives in the presence of the appropriate carboxylic acid.

$$C_4H_3O{-}CHO \xrightarrow[R'COOH]{RCN} C_4H_3O{-}CH(OCOR'){-}CONHR \xrightarrow[EtOH]{KOH} C_4H_3O{-}CHOH{-}CONHR$$

I II

I	m.p. (°C.)	II	m.p. (°C.)
R and R′ = C_6H_5	145	R = C_6H_5	126–127
R = C_6H_5, R′ = *o*-C_6H_4OH	175	R = *p*-C_6H_4OEt	150–151
R = *p*-C_6H_4OEt, R′ = *o*-C_6H_4OH	190		
R = *p*-C_6H_4OEt, R′ = C_6H_5	179–180		
R = *p*-C_6H_4OEt, R′ = CH_3	164		

β-(2-Furyl)lactic acid [3-(2-furyl)-2-hydroxypropionic acid]:

$$C_4H_3O{-}CH_2CHOH{-}COOH$$

m.p. 95–96°; $[\alpha]_D^{18}$ +27.36°; sp. gr. 1.0043; by the action of proteus bacteria on D,L-furylalanine.[61]

3-Furfuryl-4-hydroxyvaleric acid: obtained in the form of the hydrazide, V (m.p.

[61] Sasaki and Otsuka, *Biochem. Z.*, **135**, 504 (1923); *C. A.*, **17**, 2725 (1923).

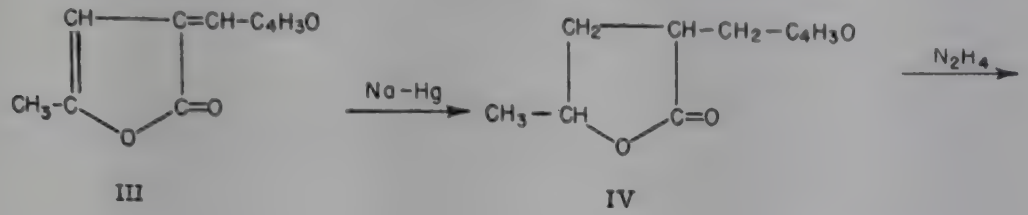
[62] Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896).

[63] Mironescu and Ioanid, *Bul. soc. chim. Romania*, **17**, 107 (1935); *C. A.*, **30**, 1053 (1936).

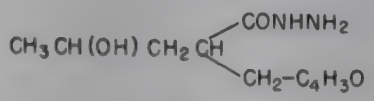
[64] Ziering and Buck, *Jubilee Vol. Emil Barell*, **1946**, 378; *C. A.*, **42**, 3533 (1948).

[65] Ridi, *Gazz. chim. ital.*, **71**, 462 (1941); *C. A.*, **37**, 1123 (1943).

138–139°) by the action of hydrazine on the corresponding lactone, IV (b.p. 85° at 0.1 mm.) derived from 2-furfurylidene-4-methyl-3-butenoic γ-lactone, III.[66] The preparation of III is described elsewhere (p. 627).



III IV



V

5-(2-Furyl)-5-hydroxyvaleric acid: $C_4H_3O—CHOH—(CH_2)_3—COOH$; **ethyl ester,** b.p. 87–95° (0.4 mm.), n_D^{20} 1.4741, obtained by catalytic hydrogenation of ethyl 5-furyl-5-hydroxy-2-pentenoate, (b.p. 101–107° (1 mm.), n_D^{20} 1.4973, unstable) derived from furfural and ethyl 4-bromocrotonate by the Reformatsky reaction.[67]

3-(2-Furyl)-3-hydroxy-2,2-dimethylvaleric acid:

$$C_4H_3O—C(OH)(C_2H_5)C(CH_3)_2—COOH$$

ethyl ester obtained in low yield by the action of EtMgBr on ethyl 2-(2-furoyl)-isobutyrate. No constants given.[68]

1-(Furyl-phenyl-hydroxymethyl)-1-cyclopropanecarboxylic acid:

$$C_4H_3O—C(OH)(C_6H_5)—C(CH_2—CH_2)—COOH$$

ethyl ester, b.p. 180° (18 mm.), obtained by treatment of ethyl 1-furoyl-1-cyclopropanecarboxylate with PhMgBr.[68]

A few derivatives of β-furylglycidic acid have been described, prepared by condensation of furfural or furyl methyl ketone with α-haloalkanoic esters by means of sodium or sodium ethoxide.

$$C_4H_3O—COR + R'CHBr—COOEt \xrightarrow{EtONa} C_4H_3O—C(R)(O)—C(R')—COOEt$$

β-(2-Furyl)glycidic acid [3-(2-furyl)-2,3-epoxypropionic acid]:

$$C_4H_3O—CH(O)—CH—COOH$$

methyl ester, b.p. 95° (2 mm.)[1]; **ethyl ester,** b.p. 114–117° (5 mm.), d_4^{20} 1.1762, n_D^{20} 1.5060.[68] With aqueous oxalic acid, the esters are decomposed into furylacetaldehyde;

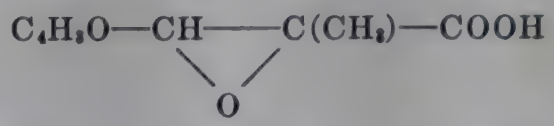
[66] Russell, Todd and Waring, *Biochem. J.*, **45**, 530 (1949).

[67] English and Gregory, *J. Am. Chem. Soc.*, **69**, 2123 (1947).

[68] Asahina and Fujita, *J. Pharm. Soc. Japan*, **490**, 1084 (1922); *C. A.*, **17**, 2578 (1923).

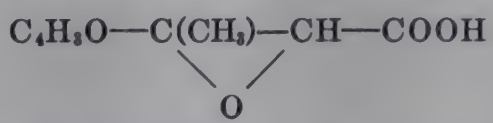
with hydroxylamine hydrochloride, they give the oxime of the preceding aldehyde.

β-(2-Furyl)-α-methylglycidic acid [3-(2-furyl)-2-methyl-2,3-epoxypropionic acid]:



methyl ester, b.p. 112–116° (9 mm.); **ethyl ester,** b.p. 150–151° (30 mm.). Obtained in good yield by condensation of furfural with α-halopropionic ester under the influence of sodium ethoxide or sodium.[69, 70]

β-(2-Furyl)-β-methylglycidic acid [3-(2-furyl)-3-methyl-2,3-epoxypropionic acid]:

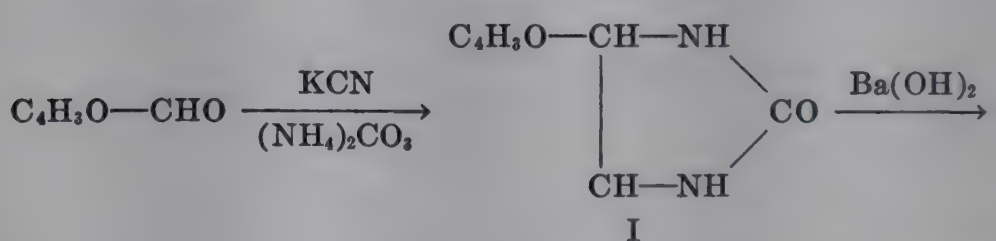


ethyl ester, obtained in 42 per cent yield from furyl methyl ketone and ethyl bromoacetate using sodium ethoxide as the condensing agent.[71]

Amino Acids

No amino acid possessing a furan nucleus has ever been found as a natural product. Indeed, only a few of them have been synthesized.

An early attempt to prepare furylglycine, II, was reported by Schmelz and Beilstein[72] who had hoped to isolate the corresponding nitrile by treatment of hydrofuramide with hydrogen cyanide. This attempt was unsuccessful, and it is only in recent years that a method of synthesis of the acid has been described. This involves hydrolysis of furylhydantoin, I, m.p. 101°,[73] 147°,[74] derived from furfural by the action of potassium cyanide and ammonium carbonate.[73]



I



II

D,L-Furylalanine, V, has been prepared in good yield by Sasaki[75] who condensed furfural with glycine anhydride (2,5-diketopiperazine) and obtained the difurfurylidene compound, III, which on reduction with sodium amalgam, was converted into 3,6-difurfuryl-2,5-diketopiperazine, IV.

[69] Darzens, *Compt. rend.*, **142**, 214 (1906).

[70] Wolf (to Knoll A.-G. Chemische Fabriken) Ger. Pat. 702,007 (1941); *C. A.*, **36**, 95 (1942).

[71] Kipnis, Levy and Ornfelt, *J. Am. Chem. Soc.*, **70**, 4265 (1948).

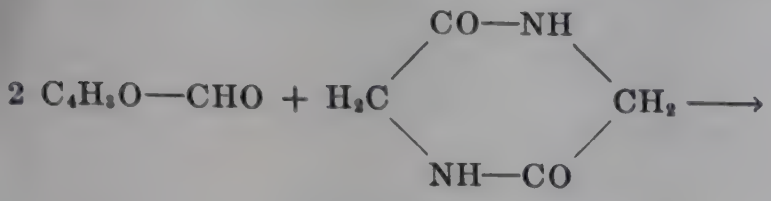
[72] Schmelz and Beilstein, *Ann. suppl.*, **3**, 275 (1864).

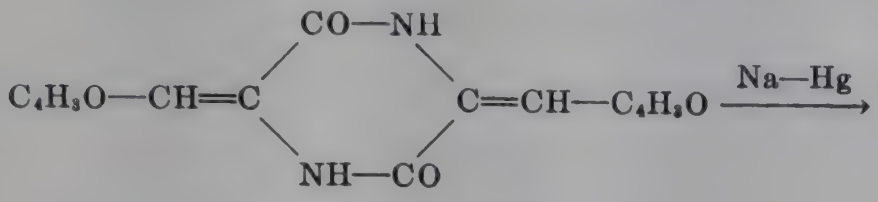
[73] Harvill and Herbst, *J. Org. Chem.*, **9**, 21 (1944).

[74] Henze and Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942).

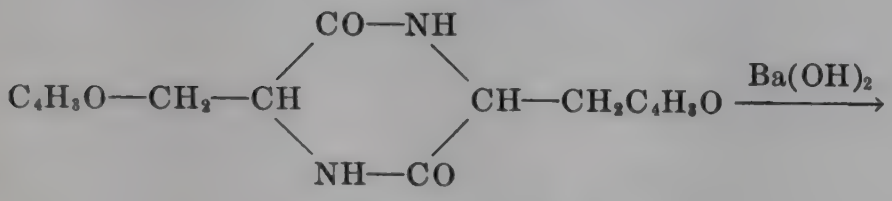
[75] Sasaki, *Ber.*, **54**, 2056 (1921).

Splitting with hot, aqueous barium hydroxide produced furylalanine which had been isolated previously by Flatow[76] by hydrolysis of the reduction product of furfurylidenehippuric acid. V has also been synthesized by

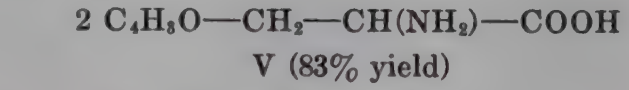




III (84% yield)



IV (95% yield)



V (83% yield)

hydrolysis of furfurylhydantoin, $C_4H_3O—CH_2CH(CO—NH)—NH—CO$, obtained by reduction of furfurylidenehydantoin with sodium amalgam[77]; from the oxime of furylpyruvic acid derived from furfural and rhodanine,[5] and by alkaline fission of ethyl 2-acetamido-2-cyano-3-(2-furyl)propionate, $C_4H_3O—CH_2C(CN)(NHAc)—COOEt$, which was synthesized from furfuryl chloride and ethyl cyanoacetamidoacetate under influence of sodium ethoxide.[78]

2-Furylglycine (furyl-aminoacetic acid): II; m.p. 212–213° (dec.) in 52 per cent yield by hydrolysis of furylhydantoin. With phenyl isocyanate, it is converted into the **phenylureido derivative,** $C_4H_3O—CH(COOH)—NHCONHC_6H_5$, m.p. 147° (dec.). From the latter, it was hoped to obtain 5-furyl-3-phenylhydantoin by cyclization, however treatment with hydrochloric acid produced extensive resinification and it was not possible to isolate the expected product.[78]

3-(2-Furyl)alanine (3-furyl-2-aminopropionic acid): V; m.p. 252° (dec.), 260° (dec.). The **phenylureido derivative,** produced by the action of phenyl isocyanate, melts at 162–163°,[75] or 177–178°.[5] **N-β-naphthalenesulfonyl derivative,** decomposes completely at 222°[75]; **N-benzoyl derivative,** m.p. 163°,[76] or 149–150°[77]; the **anhydride,** 3,6-difuryl-

[76] Flatow, *Z. physiol. Chem.*, **64**, 367 (1910); *C. A.*, **5**, 1459 (1911).
[77] Deulofeu, *Anales asocn. quim. Argentina*, **20**, 190 (1932); *C. A.*, **27**, 3709 (1933).
[78] Herz, Dittmer and Cristol, *J. Biol. Chem.*, **171**, 383 (1947).

2,5-diketopiperazine (IV), m.p. 216°.[75] The effect of D,L-furylalanine on the growth of micro-organisms was studied by Clark and Dittmer.[79]

3-[5-(Hydroxymethyl)furyl]alanine: $HOCH_2—C_4H_2O—CH_2CH(NH_2)COOH$; m.p. 295°; from (hydroxymethyl)furfurylhydantoin (m.p. 167°) by hydrolysis with barium hydroxide.[80]

3-(2-Furyl)-3-aminopropionic acid: $C_4H_3O—CH(NH_2)—CH_2COOH$; m.p. 205–206°; isolated from the complex mixture obtained by heating furylacrylic acid with an excess of hydroxylamine. **Anilide,** m.p. 92°.[81, 82]

3-(2-Furyl)-3-amino-2-benzamidopropionic acid:

$$C_4H_3O—CH(NH_2)—CH(NH—COC_6H_5)—COOH$$

m.p. 173.5°; obtained as one product of the reaction of furfurylidenehippuric acid with hydroxylamine.[81]

3-(2-Furyl)-3-ureido-2-benzamidopropionic acid:

$$C_4H_3O—CH(NHCONH_2)—CH(NH—COC_6H_5)—COOH$$

m.p. 196°, by the action of potassium cyanide on the preceding acid, followed by careful hydrolysis with dilute hydrochloric acid.[81]

Keto Acids and Their Derivatives

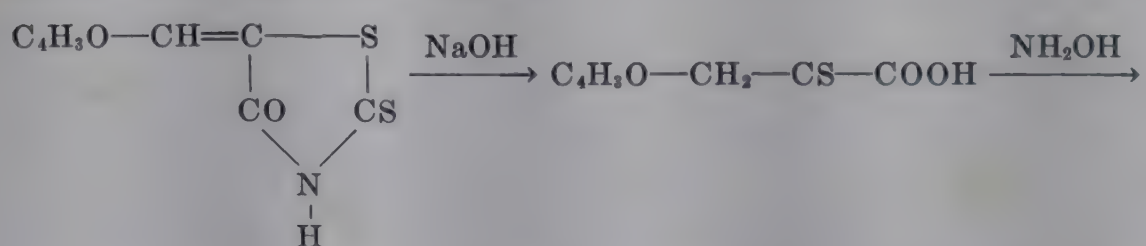
α-Keto Acids. Furoylformic acid, I (R = H), has been synthesized by hydrolysis of the corresponding nitrile, derived from furoyl chloride and hydrogen cyanide in pyridine.[59, 1, 2] Similarly, the homologous 5-methyl-2-furoylformic acid is obtained from 5-methyl-2-furoyl chloride.[13]

$$2,5—C_4H_2O—(R)(COCl) \xrightarrow[C_5H_5N]{HCN} 2,5—C_4H_2O—(R)(COCN) \xrightarrow{HCl}$$

$$2,5—C_4H_2O—(R)(COCOOH)$$

I

The sole remaining α-keto acid which has been described is furylpyruvic acid, II. This was synthesized from furfurylidenerhodanine (m.p. 229–231°) by hydrolysis to the thioketo acid, which was converted into the keto acid by way of the oxime.[83]



$$C_4H_3O—CH_2—C(NOH)—COOH \xrightarrow{H_2SO_3} C_4H_3O—CH_2—CO—COOH$$

II

[79] Clark and Dittmer, *J. Biol. Chem.*, **173**, 313 (1948).
[80] Iseki, *Z. physiol. Chem.*, **216**, 127 (1933); *C. A.*, **27**, 2953 (1933).
[81] Posner and Sichert, *Ber.*, **63**, 3078 (1930).
[82] Posner, *Ann.*, **389**, 1 (1912).
[83] Gränacher, Gerö and Schelling, *Helv. Chim. Acta*, **7**, 575 (1924).

Furoylformic acid (furylglyoxylic acid): $C_4H_3O—CO—COOH$; m.p. 94–95°, 97–98.5°; b.p. 105° (1 mm.)[59, 1] (see also [84]). The corresponding **nitrile,** furoyl cyanide, boils at 67–71° (0.7 mm.)[2]; ***p*-methylanil,** m.p. 102°, by treatment of furyl-N-*p*-tolyl nitrone with alcoholic potassium cyanide[85]; ***p*-dimethylaminoanil,** m.p. 180°.[84]

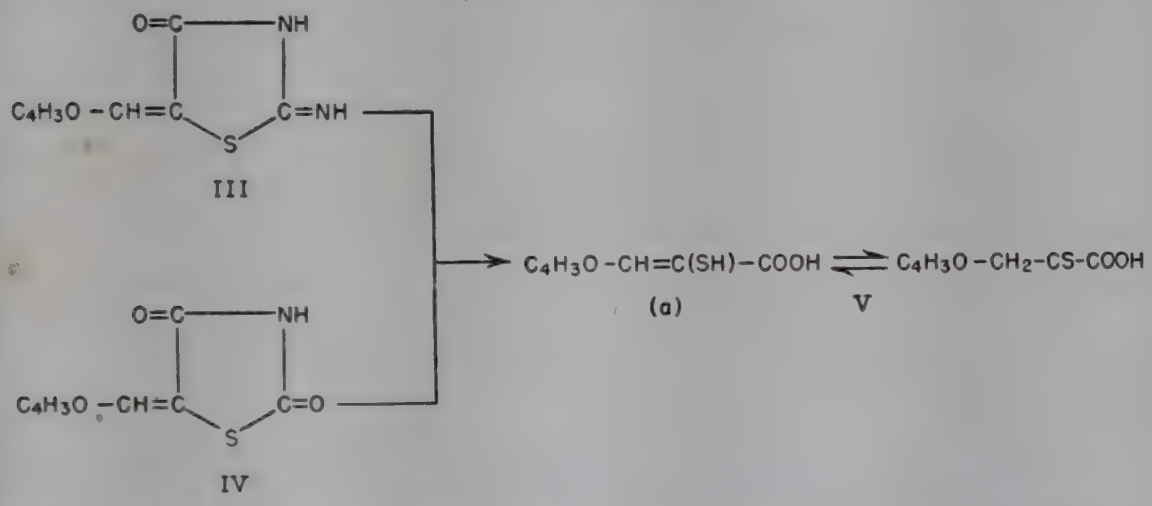
5-Methyl-2-furoylformic acid (5-methyl-2-furylglyoxylic acid):

$$CH_3—C_4H_2O—COCOOH$$

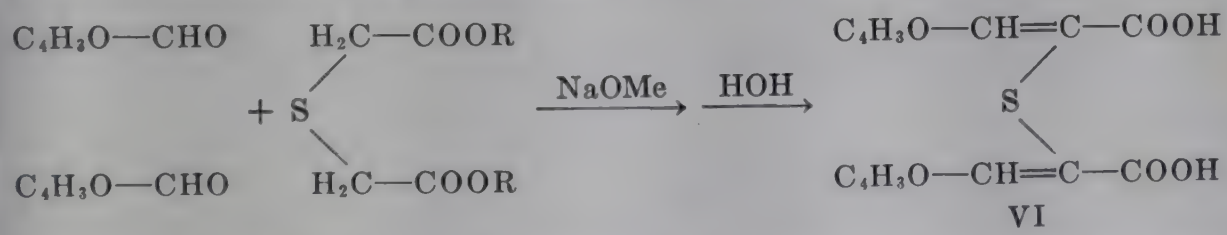
m.p. 90–91°, b.p. 100° (1 mm.). The corresponding **nitrile,** m.p. 55°, b.p. *ca.* 100° (11 mm.).[13]

Furylpyruvic acid (furfurylglyoxylic acid): $C_4H_3O—CH_2COCOOH$; m.p. 131° (dec.), by splitting the oxime with sulfurous acid.[83] The **oxime** (two forms, m.p. 127–128°, 143.8–144°) is obtained from the thioketo acid, furylthiopyruvic acid, according to the scheme illustrated above[4] (see also [5]).

Furylthiopyruvic acid (3-furyl-2-thioketopropionic acid): V; m.p. 114.6–115°, by hydrolysis of furfurylidenerhodanine as illustrated above,[4] of furfurylidenepseudothiohydantoin, III (m.p. 244° (dec.)),[86] and of 5-furfurylidene-2,4-thiazolidinedione, IV.[86] Related to form Va is difurfurylidenethiodiacetic acid, VI, m.p. 207° (dec.)



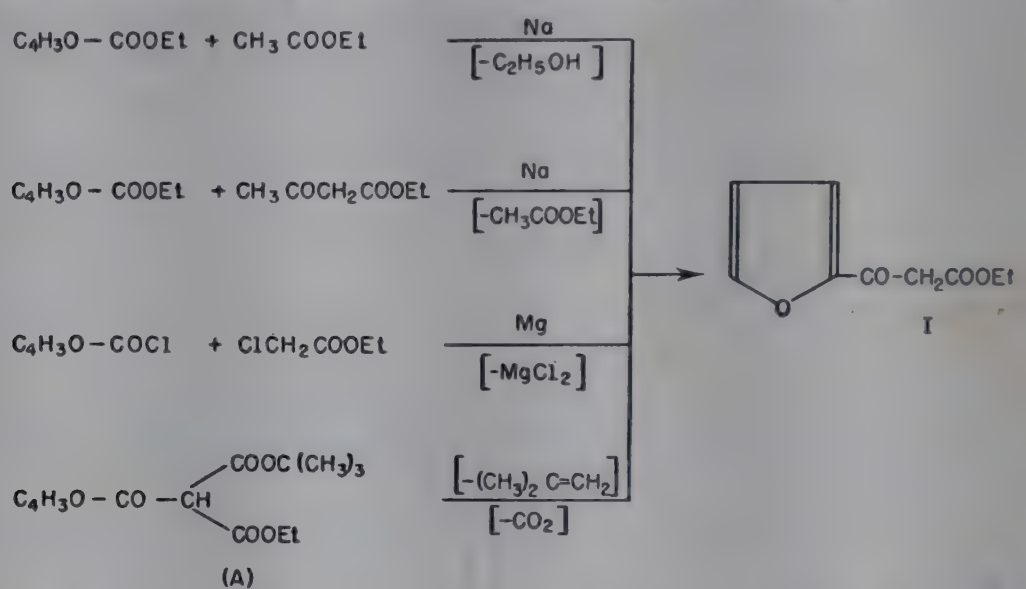
obtained by condensation of furfural with thiodiglycollic ester under the influence of sodium methoxide. The dimethyl ester of VI, m.p. 129–131°.[87]



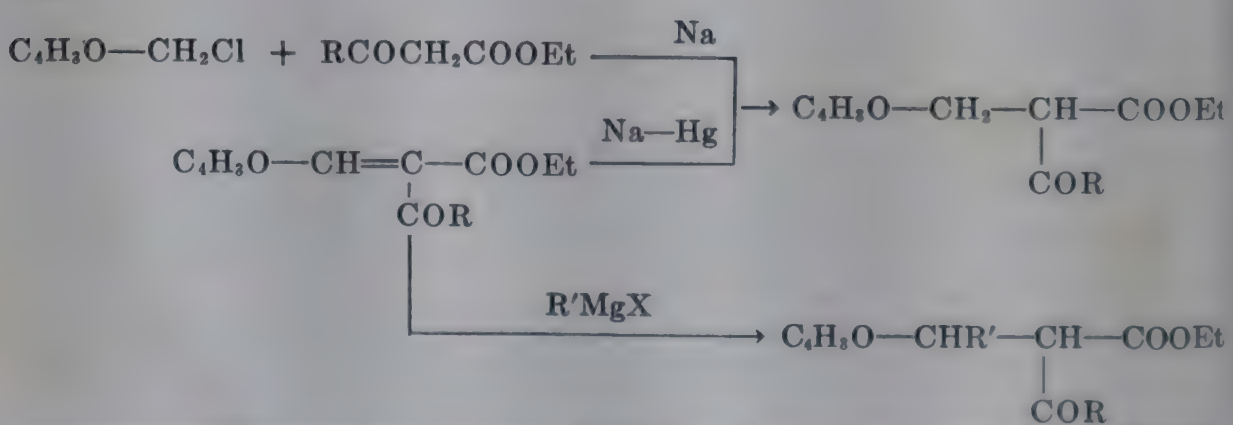
β-Keto Acids. A number of β-keto esters containing the furan ring are known. The simplest of these is ethyl 2-furoylacetate, I, which was first reported by Bouveault[88, 89] and shortly thereafter by Sandelin.[90] The mode

[84] Kröhnke, *Chem. Ber.*, **80**, 298 (1947).
[85] Bellavita, *Gazz. chim. ital.*, **70**, 584 (1940); *C. A.*, **35**, 2127 (1941).
[86] Libermann, Himbert and Hengl, *Bull. soc. chim. France*, **1948**, 1120.
[87] Backer and Stevens, *Rec. trav. chim.*, **59**, 899 (1940).
[88] Bouveault, *Compt. rend.*, **125**, 1184 (1897).
[89] Bouveault, *Bull. soc. chim.* (*3*), **25**, 435 (1901).
[90] Sandelin, *Ber.*, **33**, 492 (1900).

of preparation, condensation of ethyl 2-furoate with ethyl acetate under the influence of sodium, was later adopted by several other investigators,[91, 92, 93, 94] and under the conditions employed by Barger, Robinson and Smith,[95] produces ethyl furoylacetate in 93 per cent yield. The product has also been obtained by heating ethyl furoate with sodioacetoacetic ester,[96] by the action of magnesium on a mixture of furoyl chloride and chloroacetic ester,[63] and by the general procedure developed by Breslow, Baumgarten and Hauser[97] wherein ethyl *t*-butyl malonate is acylated with furoyl chloride and the resulting product (A) is decomposed in acidic medium (loses isobutylene) to ethyl hydrogen furoylmalonate which readily loses carbon dioxide to give the β-keto monocarboxylic ester.



Homologous β-keto esters are obtained (1) by substituting homologs of ethyl furoate in the first procedure illustrated above, (2) by introduction of one or two alkyl groups into the reactive methylene group of furoylacetic ester by reacting the sodio compound with alkyl halides, (3) from furfurylideneacylacetic esters by reduction or by the action of the Grignard reagent, and (4) by treatment of sodioacetoacetic ester with furfuryl chloride.



[91] Torrey and Zanetti, *Am. Chem. J.*, **36**, 539 (1906).
[92] Torrey and Zanetti, *Am. Chem. J.*, **44**, 391 (1910).

2-Furoylacetic acid: $C_4H_3O—COCH_2COOH$; unknown in the free state. **Ethyl ester,** b.p. 113–114° (1 mm.), 143–145° (10 mm.); d^{17} 1.165; n_D^{16} 1.5055; a pale yellow to colorless oil which darkens on standing.[88, 89, 90, 91, 92, 95, 97] Hydrolysis of the ester in aqueous acidic medium produces furyl methyl ketone.[88, 89, 90, 94] With nitrous acid, the ester is converted into ethyl oximino-furoylacetate,

$$C_4H_3O—CO—C(=NOH)—COOEt$$

m.p. 128–129°.[91, 92] Condensation of the ester with chloracetic ester gives furoylsuccinic ester, $C_4H_3O—COCH(CH_2COOEt)COOEt$, m.p. 56°.[33] **Ester oxime,** m.p. 131–132°; anhydride of oxime, 3-(2-furyl)isoxazolone, m.p. 148–149° (dec.)[91, 92]; **ester semicarbazone,** m.p. 142–144°.[91, 92] With hydrazines, the ester forms substituted pyrazolones (see discussion which follows). Na, K and Cu salts of the ester are described by Torrey and Zanetti[91, 92]; **amide:** m.p. 159°[63]; **N-substituted amides:** *p*-toluidide, m.p. 142–144°; *p*-anisidide, m.p. 108–109°; *p*-phenetidide, m.p. 125–126°; *p*-chloroanilide, m.p. 131–133°; 2,5-dimethoxyanilide, m.p. 121–123°; 2,5-diethoxyanilide, m.p. 118–120°; 2-methyl-5-chloroanilide, m.p. 131–133°; 2-methoxy-5-chloroanilide, m.p. 116–117°; 2,5-diethoxy-4-chloroanilide, m.p. 154–156°; 2,5-dimethyl-4-chloroanilide, m.p. 147–149°; 2-methoxynaphthylamide, m.p. 173–175°. These substituted amides are reported to be useful intermediates for the preparation of azo dyestuffs[98] (see also [98a]). For the behavior of furoylacetic ester in animal metabolism, see Friedman.[99]

2-(2-Furoyl)propionic acid: $C_4H_3O—COCH(CH_3)—COOH$. **Ethyl ester,** b.p. 143° (11 mm.) by alkylation of ethyl furoylacetate using methyl iodide and sodium ethoxide; **amide,** m.p. 183°. The ester was saponified to furyl ethyl ketone by heating with dilute HCl.[63]

2-(2-Furoyl)isobutyric acid: $C_4H_3O—COC(CH_3)_2—COOH$. **Ethyl ester,** b.p. 150° (20 mm.) by methylation of the preceding acid; **amide,** m.p. 164°. The ester was split to furyl *i*-propyl ketone[63] (see also [100]).

2-(2-Furoyl)butyric acid: $C_4H_3O—COCH(C_2H_5)—COOH$. **Ethyl ester,** b.p. 148° (14 mm.), by ethylation of ethyl furoylacetate with ethyl bromide and sodium ethoxide; **amide,** m.p. 188°. The ester was hydrolyzed to furyl propyl ketone.[63]

2-(2-Furoyl)-2-methylbutyric acid: $C_4H_3O—COC(CH_3)(C_2H_5)—COOH$. **Ethyl ester** (no constants given) prepared by alkylating 2-(2-furoyl)propionic ester with ethyl bromide in usual manner. The ester gave furyl *sec*-butyl ketone on hydrolytic fission with dilute HCl.[63]

2-Furoyldiethylacetic acid: $C_4H_3O—COC(C_2H_5)_2—COOH$. **Ethyl ester,** b.p. 177° (25 mm.) by ethylation of 2-(2-furoyl)butyric ester. Saponification of the ester in dilute HCl produced furyl diethylmethyl ketone.[63]

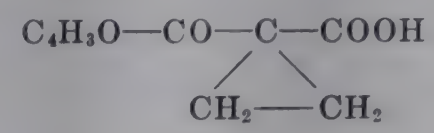
(3-Methyl-2-furoyl)acetic acid (Elsholtzioylacetic acid): $CH_3—C_4H_2O—COCH_2COOH$. **Ethyl ester,** b.p. 145–150° (15 mm.), d_4^{17} 1.1437, n_D^{19} 1.50044, by condensation of ethyl

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[93] Wahl and Doll, *Bull. soc. chim.* (4), **13,** 265 (1913).
[94] Ciusa, *Gazz. chim. ital.*, **52,** 43 (1922); *C. A.*, **17,** 1478 (1923).
[95] Barger, Robinson and Smith, *J. Chem. Soc.*, **1937,** 718.
[96] McElvain and Weber, *J. Am. Chem. Soc.*, **63,** 2192 (1941).
[97] Breslow, Baumgarten and Hauser, *J. Am. Chem. Soc.*, **66,** 1286 (1944).
[98] Zwilgmeyer (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,064,331-2 (1936); *C. A.*, **31,** 833–834 (1937).
[98a] Andrisano *et al.*, *Boll sci. facoltà chim. ind. Bologna*, **8,** 4, 10, 18 (1950); *C. A.*, **44,** 9675–9676 (1950); *Ann. chim. Rome*, **40,** 439 (1950); *C. A.*, **45,** 8775 (1951).
[99] Friedman, *Biochem. Z.*, **35,** 40 (1911); *C. A.*, **6,** 398 (1912).
[100] Monoya, *J. Pharm. Soc. Japan*, **447,** 357 (1919); *C. A.*, **13,** 2516 (1919).

3-methyl-2-furoate with ethyl acetate by means of sodium. The ester failed to form the oxime with hydroxylamine, but gave the isoxazolone derivative, m.p. 95°.[101]

1-(2-Furoyl)-1-cyclopropanecarboxylic acid:



Ethyl ester, b.p. 148–149° (16 mm.), by treatment of ethyl furoylacetate with dibromoethane and sodium ethoxide; **amide:** m.p. 162°. Cleavage of the ester with dilute HCl produced furyl cyclopropyl ketone.[63]

α-(2-Furyl)acetoacetic ethyl ester: $C_4H_3O—CH(COCH_3)—COOC_2H_5$; b.p. 98–100° (8 mm.), in 53 per cent yield by reaction of ethyl furylacetate with ethyl acetate in the presence of sodium.[6]

α-Furfurylacetoacetic ethyl ester: $C_4H_3O—CH_2CH(COCH_3)—COOC_2H_5$; b.p. 111–111.5° (4 mm.); d_{20}^{20} 1.10562, d_4^{20} 1.10366; n_D^{20} 1.4718; obtained in 61 per cent yield by condensation of furfuryl chloride with sodioacetoacetic ester,[22] and also by reduction of furfurylideneacetoacetic ester using sodium amalgam.[102] Reaction of the ester with a variety of hydrazines to form substituted pyrazolones was carried out by Dohrn and Hamann.[102] Hydrolytic fission of the ester in concentrated alkaline medium produces 3-(2-furyl)propionic acid in good yield.[22] **Anilide:** m.p. 118–121°.[102]

α-Furfuryl-furoylacetic ethyl ester*: $C_4H_3O—CH_2CH(CO—C_4H_3O)—COOC_2H_5$; b.p. 196–202° (15 mm.) by catalytic hydrogenation of ethyl furfurylidene-furoylacetate. The ester was condensed with phenylhydrazine to obtain the appropriately substituted pyrazolone.[102]

α-Furfuryl-benzoylacetic ethyl ester: $C_4H_3O—CH_2CH(CO—C_6H_5)—COOC_2H_5$; b.p. 168–172° (3 mm.), by reduction of furfurylidenebenzoylacetic ester. Used for the synthesis of substituted pyrazolones.[102]

α-Acetyl-β-(2-furyl)valeric ethyl ester:

$$C_4H_3O—CH(C_2H_5)—CH(COCH_3)—COOC_2H_5$$

b.p. 152° (21 mm.), by the action of EtMgI on furfurylideneacetoacetic ester. Ketonic splitting of the ester gives 4-(2-furyl)-2-hexanone.[45]

α-Acetyl-β-(2-furyl)caproic ethyl ester:

$$C_4H_3O—CH(C_3H_7)—CH(COCH_3)—COOC_2H_5$$

b.p. 155° (15 mm.). Prepared as in the preceding case using PrMgBr. The ester was split to obtain 4-(2-furyl)-2-heptanone.[45]

α-Acetyl-β-(2-furyl)-β-phenylpropionic ethyl ester:

$$C_4H_3O—CH(C_6H_5)—CH(COCH_3)—COOC_2H_5$$

b.p. 195° (14 mm.), as in the preceding case, using PhMgBr. Ketonic hydrolysis of the ester produces 4-(2-furyl)-4-phenyl-2-butanone.[45]

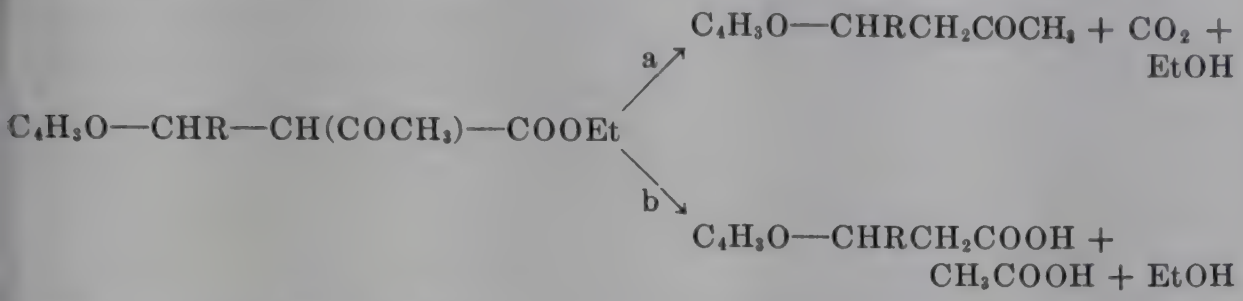
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* Dohrn and Hamann refer to this compound as "α-furfuryl-furyl-aceto-acetic acid." See remarks under furfurylidene-furoylacetic acid, p. 628.

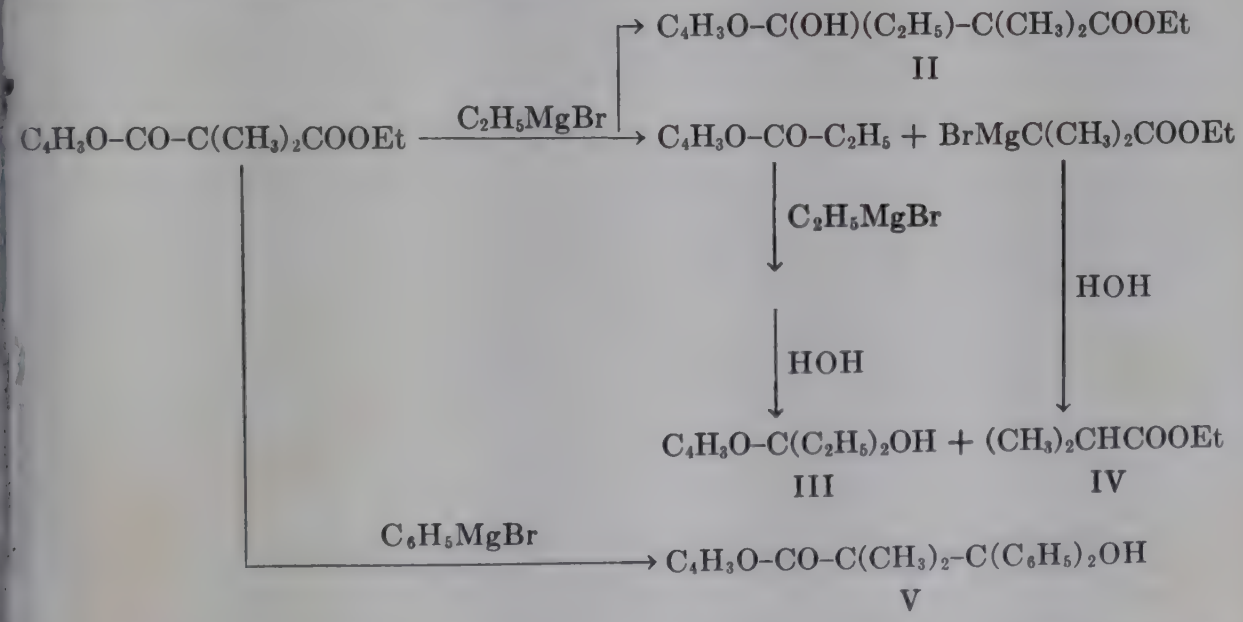
[101] Asahina, Murayama, Shibata, Kariyone, Kuwada and Asano, *Acta Phytochim.*, **2**, 1 (1924); *C. A.*, **19**, 1139 (1925).

[102] Dohrn and Hamann (to Schering Corp.), U. S. Pat. 2,272,739 (1942); *C. A.*, **36**, 3632 (1942).

The free β-keto acids are unknown. Hydrolysis of the esters results in the normal "ketone" or "acid" splitting, depending upon the experimental conditions. In acidic or dilute alkaline medium (a) they are converted predominantly to the expected keto-furans[88, 89, 90, 94, 45, 63] whereas with strong alkali (b), fission takes place primarily at the ketone group with formation of carboxylic acids.[22]



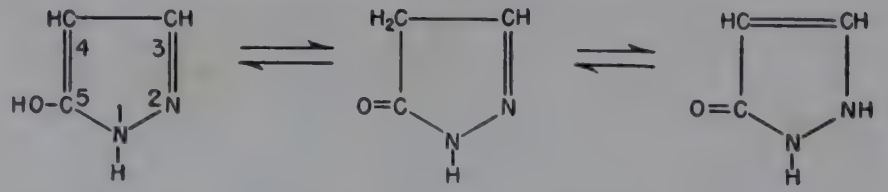
Mironescu and Ioanid[63] treated a number of the esters with the Grignard reagent and obtained a variety of tertiary alcohols possessing either ketone or ester groups depending upon the point of attack. In the particular case of the action of ethylmagnesium bromide on 2-furoylisobutyric ester they obtained some of the expected β-hydroxy ester, II, but in addition splitting occurred to a certain extent, resulting finally in the formation of furyldiethylcarbinol, III, and *i*-butyric ester, IV. On the other hand, when the same ester was treated with phenylmagnesium bromide, no splitting was observed[c] and addition was confined to the ester group to produce 1,1-diphenyl-2-methyl-2-furoylpropyl alcohol, V.



When the β-keto ester possessed an alpha hydrogen atom (the monoalkylated esters), the Grignard apparently reacted to form an alkoxide of

[c] Splitting did take place when furoyldiethylacetic ester was treated with PhMgBr, since furyldiphenylcarbinol is reported as the product.[63]

Table 2. 5-Pyrazolones Containing the Furan Nucleus

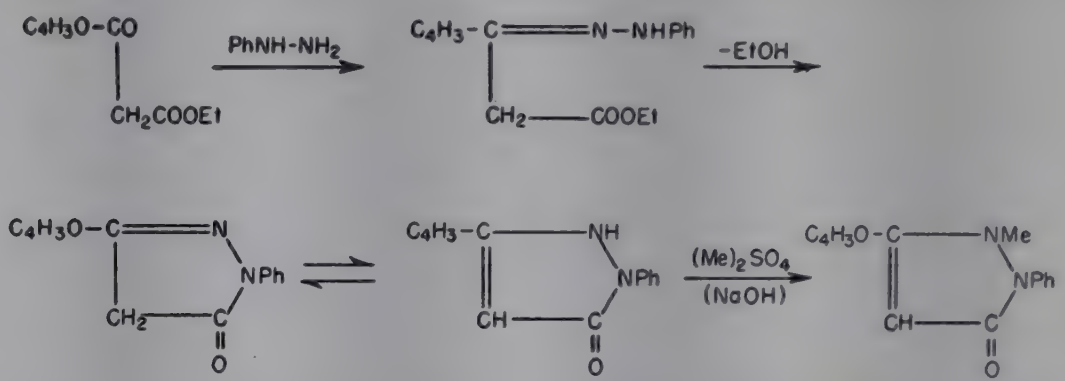


Reactants	Substituted 5-pyrazolone	M.p. (°C.)	Ref.
Furoylacetic ester + $H_2N—NH_2$	I, 3-(2-furyl)- **derivatives**, m.p., °C. picrate, 192 1-acetyl-, 153–154 1,2-diacetyl-, 102 4-benzylidene-, >300 4-azobenzene-, 182–183	223 (dec.)	92, 103
Furoylacetic ester + $(C_6H_5)NH—NH_2$	II, 1-phenyl-3-(2-furyl)- **derivatives**, m.p., °C. hydrochloride, 122–123 2-acetyl-, 69–72 benzoate, 113–114 4-isonitroso-, 183–184 4-benzylidene-, 210–212 (dec.) 4-azobenzene-, 165 4-β-azonaphthalene-, 202–203	178–179	90, 92, 103, 97
II + CH_3I	III, 1-phenyl-2-methyl-3-(2-furyl)- **derivatives**, m.p., °C. hydrochloride, 197–198 (dec.) hydrobromide, 194 (dec.)	—	92, 103

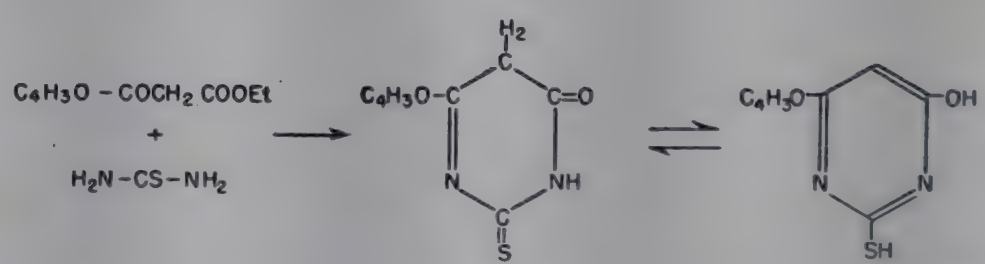
	hydriodide, 192–193 (dec.) picrate, 157–158 (dec.) 4-nitroso-, 185 (dec.)		
Furoylacetic ester + $(p\text{-}BrC_6H_4)NH—NH_2$	IV, 1-*p*-bromophenyl-3-(2-furyl)-	160–161	92, 103
Furoylacetic ester + $(p\text{-}SO_3NaC_6H_4)NH—NH_2$	V, 1-*p*-sulfophenyl-3-(2-furyl)-	>295	92, 103
Furoylacetic ester + $(m\text{-}NO_2C_6H_4)NH—NH_2$	VI, 1-*m*-nitrophenyl-3-(2-furyl)-	174–175	92, 103
α-Furfurylacetoacetic ester + $(C_6H_5)NHNH_2$	VII, 1-phenyl-3-methyl-4-furfuryl-	131–133	102
α-Furfurylacetoacetic ester + $(C_6H_5)NHNH(CH_3)$	VIII, 1-phenyl-2,3-dimethyl-4-furfuryl-	89–91	102
VII + $(CH_3)_2SO_4$	VIII	89–91	102
α-Furfurylacetoacetic ester + $(p\text{-}CH_3C_6H_4)NHNH_2$	IX,1-*p*-tolyl-3-methyl-4-furfuryl-	118–120	102
IX + $(CH_3)_2SO_4$	X, 1-*p*-tolyl-2,3-dimethyl-4-furfuryl-	90–92	102
α-Furfurylacetoacetic ester + $(p\text{-}NO_2C_6H_4)NHNH_2$	XI, 1-*p*-nitrophenyl-3-methyl-4-furfuryl-	169–170	102
XI + $(CH_3)_2SO_4$	XII, 1-*p*-nitrophenyl-2,3-dimethyl-4-furfuryl-	74–76	102
α-Furfurylacetoacetic ester + $(p\text{-}BrC_6H_4)NHNH_2$	XIII, 1-*p*-bromophenyl-3-methyl-4-furfuryl-	170–172	102
XIII + $(CH_3)_2SO_4$	XIV, 1-*p*-bromophenyl-2,3-dimethyl-4-furfuryl-	103–105	102
α-Furfurylacetoacetic ester + $(p\text{-}SO_3NaC_6H_4)$-$NHNH_2$	XV, 1-*p*-sulfophenyl-3-methyl-4-furfuryl-	no m.p.	102
α-Furfurylacetoacetic ester + $(p\text{-}CH_3CONHC_6H_4)$-$NHNH_2$	XVI, 1-*p*-acetamidophenyl-3-methyl-4-furfuryl-	244–246	102
α-Furfurylacetoacetic ester + $(p\text{-}C_2H_5OC_6H_4)$-$NHNH_2$	XVII, 1-*p*-ethoxyphenyl-3-methyl-4-furfuryl-	102–104	102
XVII + $(CH_3)_2SO_4$	XVIII, 1-*p*-ethoxyphenyl-2,3-dimethyl-4-furfuryl-	91–93	102
α-Furfurylacetoacetic ester + $(C_6H_{11})NHNH_2$	XIX, 1-cyclohexyl-3-methyl-4-furfuryl-	142	102
XIX + $(CH_3)_2SO_4$	XX, 1-cyclohexyl-2,3-dimethyl-4-furfuryl-	45–48	102
α-Furfurylbenzoylacetic ester + $(p\text{-}CH_3C_6H_4)$-$NHNH_2$	XXII, 1-*p*-tolyl-3-phenyl-4-furfuryl-	135–137	102
α-Furfurylbenzoylacetic ester + $(p\text{-}NO_2C_6H_4)$-$NHNH_2$	XXIII, 1-*p*-nitrophenyl-3-phenyl-4-furfuryl-	203–205	102
α-Furfurylfuroylacetic ester + $(C_6H_5)NHNH_2$	XXIV, 1-phenyl-3-(2-furyl)-4-furfuryl-	not isolated	102
XXIV + $(CH_3)_2SO_4$	XXV, 1-phenyl-2-methyl-3-(2-furyl)-4-furfuryl-	144	102

the enol form, $C_4H_3O—C(OMgX)=CRCOOEt$, which on hydrolysis regenerated the original ester.[63]

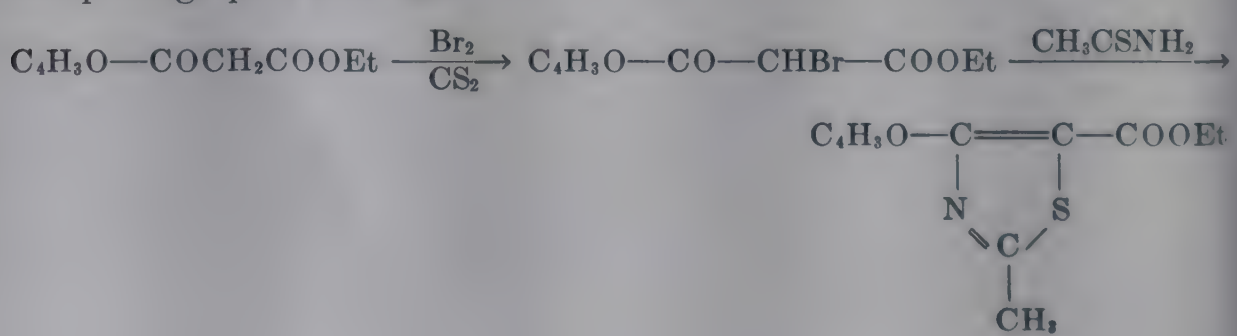
A variety of substituted 5-pyrazolones have been synthesized in the usual manner by condensation of hydrazine and its derivatives with several of the β-keto esters of the furan series. Like those derived from acetoacetic ester, these products may be alkylated, and in this way compounds related to antipyrine have been prepared. Starting with α-furfurylacylacetic esters, Dohrn and Hamann[102] obtained a number of these types which they report to be particularly active antipyretics. The reactions involved are illustrated below for the condensation of furoylacetic ester with phenylhydrazine.



Similarly, condensation with urea or thiourea produces furyl substituted uracils and thiouracils respectively. Thus, furoylacetic ester reacts with urea to give 2,4-dihydroxy-6-(2-furyl)pyrimidine, m.p. 321°,[104] and with thiourea to give the corresponding 2-mercapto-4-hydroxy derivative, m.p. 298°.[105]



Bromination of 2-furoylacetic ester and subsequent condensation with thioacetamide gives rise to 2-methyl-4-(2-furyl)-5-carbethoxythiazole (b.p. 145–150° at 20 mm.), the salts of which are useful as dye intermediates and photographic sensitizers.[106]



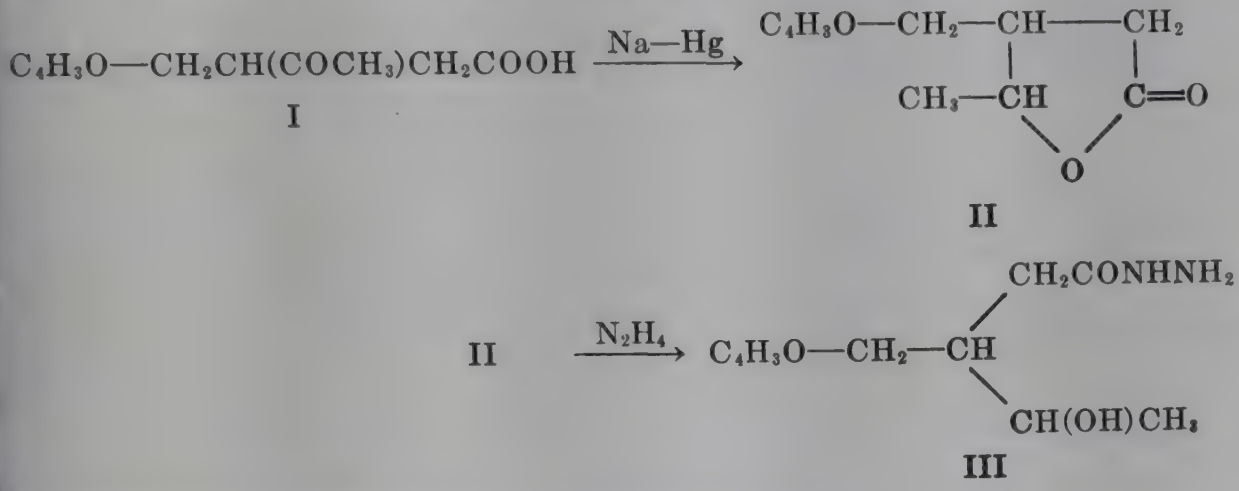
γ-Keto Acids.

β-(2-Furoyl)propionic acid [4-(2-furyl)-4-oxobutyric acid]:

$$C_4H_3O—CO—CH_2CH_2COOH$$

m.p. 113–114°, 115°. **Semicarbazone,** m.p. 184°; **ethyl ester,** m.p. 52–53°, obtained by heating furoylsuccinic ester in dilute sulfuric acid[33] and also, as the **nitrile** (m.p. 74–76°), by refluxing 2-furyl 2-dimethylaminoethyl ketone, as the hydrochloride, with aqueous potassium cyanide.[107] The nitrile, on reduction with hydrogen at room temperature over Raney nickel is reported to give rise to 2-(2-furyl)-2,3-pyrroline, m.p. 55–56°[108]; on treatment with aqueous, alcoholic hydrazine, it forms 3-oxo-6-(2-furyl)-2,3,4,5-tetrahydropyridazine, m.p. 145°.[107]

β-Furfuryllevulinic acid [4-(2-furyl)-3-acetylbutyric acid]: I; m.p. 100–101°, by reduction of β-furfurylidenelevulinic acid with sodium amalgam.[109] Reduction of I with sodium amalgam gives rise to β-furfuryl-γ-methyl-γ-butyrolactone, II (b.p. 70–75° at 0.1 mm.), which is cleaved by refluxing with ethanolic hydrazine hydrate to form β-furfuryl-γ-hydroxyvaleric hydrazide, III (m.p. 133–134°).[66]



I

δ-Furfuryllevulinic acid [6-(2-furyl)-4-oxohexanoic acid]:

$$C_4H_3O—(CH_2)_2CO(CH_2)_2COOH$$

m.p. 98°, by reduction of δ-furfurylidenelevulinic acid with sodium amalgam.[109] Oxidation with aqueous bromine and then with silver oxide cleaves the nucleus and produces *anemonic* acid, HOOC—CH=CH—CO—$(CH_2)_2$—CO—$(CH_2)_2$COOH.[109a]

β,δ-Difurfuryllevulinic acid: $C_4H_3O—(CH_2)_2COCH(CH_2—C_4H_3O)CH_2COOH$; m.p. 71–72°, by reduction of the difurfurylidene compound with sodium amalgam.[109]

Diketo Acids.

Furoylpyruvic ethyl ester: $C_4H_3O—COCH_2COCOOC_2H_5$; yellow crystals, m.p. 70°; obtained in 32 per cent yield by condensation of furyl methyl ketone with oxalic ester by means of sodium ethoxide.[71]

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[103] Torrey and Zanetti, *J. Am. Chem. Soc.*, **30,** 1241 (1908).
[104] Andrisano, *Gazz. chim. ital.*, **77,** 502 (1947); *C. A.*, **42,** 3411 (1948).
[105] Andrisano, *Ricerca sci. e ricostruz.*, **17,** 252 (1947); *C. A.*, **43,** 7929 (1949).
[106] Middleton (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,524,674 (1950).
[107] Knott, *J. Chem. Soc.*, **1947,** 1190.
[108] Knott, *J. Chem. Soc.*, **1948,** 186.
[109] Kehrer and Kleberg, *Ber.*, **26,** 345 (1893).

Furoylacetoacetic ethyl ester: $C_4H_3O—COCH(COCH_3)COOC_2H_5$; b.p. 167° (16 mm.). from furoyl chloride and sodioacetoacetic ester. Split by the action of ammonia to furoylacetic ester.[63]

Cyano Acids

3-(2-Furyl)-2-cyanopropionic acid: $C_4H_3O—CH_2—CH(CN)—COOH$; b.p. 103–104° (11 mm.); by reduction of furfurylidenecyanoacetic acid with sodium amalgam.[110]

3-(2-Furyl)-3-cyanopropionic acid: $C_4H_3O—CH(CN)—CH_2COOH$; m.p. 109°; **ethyl ester,** b.p. 174.5° (33 mm.). Prepared from furfurylidenemalonic ester and aqueous potassium cyanide in alcohol. Treatment with alkali produces furylsuccinic acid.[111]

3-(2-Furyl)-2-cyanocaproic acid: $C_4H_3O—CH(C_3H_7)—CH(CN)—COOH$; m.p. 140°; **ethyl ester,** b.p. 154° (8 mm.), in 82 per cent yield from furfurylidenecyanoacetic ester and PrMgBr.[45]

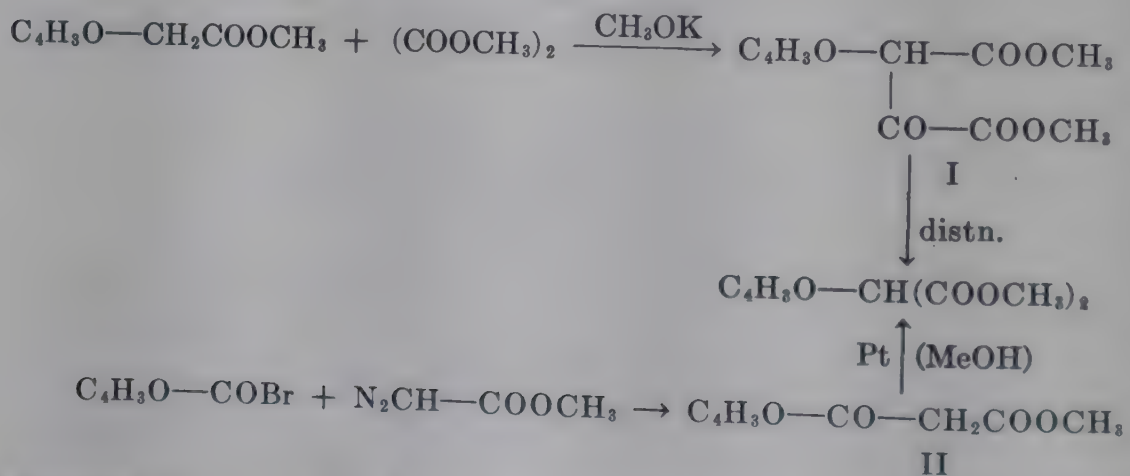
3-(2-Furyl)-2-cyano-5-methylcaproic ethyl ester:

$$C_4H_3O—CH(i\text{-}C_4H_9)—CH(CN)—COOC_2H_5$$

b.p. 171° (20 mm.) by the action of *i*-BuMgCl on furfurylidenecyanoacetic ester.[45]

Furylalkanedioic Acids

2-Furylmalonic acid: $C_4H_3O—CH(COOH)_2$; m.p. 106–107° (dec.); **dimethyl ester,** b.p. 130–132° (9 mm.); **diethyl ester,** b.p. 138° (15 mm.); **diamide,** m.p. 185–186°. Obtained, as the ester, by decomposition of furyl-oxaloacetic ester, I, on distillation,[2, 6] and also by heating a methanol solution of furoyldiazoacetic ester, II (m.p. 108°), in the presence of platinum.[2]



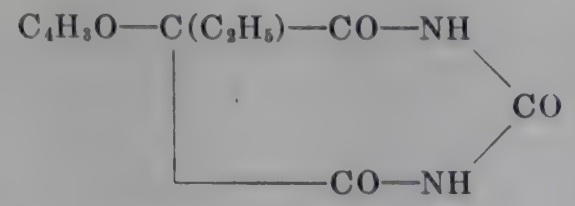
α-(2-Furyl)ethylmalonic acid: $C_4H_3O—C(C_2H_5)(COOH)_2$; **dimethyl ester,** b.p. 136–137° (14 mm.), obtained by alkylation of methyl furylmalonate using ethyl iodide and sodium methoxide. Hydrolysis of the ester and decarboxylation gives rise to 2-(2-furyl)butyric acid. Condensation of the ester with urea by means of sodium methoxide gives furylethylbarbituric acid,

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[109] Asahina and Fujita, *J. Pharm. Soc. Japan*, **448**, 471 (1919); *C. A.*, **13**, 2517 (1919).

[110] Šorm and Brandejs, *Collection Czechoslov. Chem. Communs.*, **12**, 444 (1947); *C. A.*, **43**, 2988 (1949).

[111] Sandelin, *Ber.*, **33**, 487 (1900).



m.p. 187.5–189°; b.p. 140° (0.2 mm.).[2]

α-Furfurylmalonic acid [α-(2-furylmethyl)malonic acid]: $C_4H_3O—CH_2—CH(COOH)_2$; m.p. 127°. **Diethyl ester:** b.p. 171–173° (33 mm.), d_{20}^{20} 1.11196, d_4^{20} 1.10999; n_D^{20} 1.4591; obtained in 76 per cent yield by the action of furfuryl chloride on sodiomalonic ester,[22] and in about 90 per cent yield from furfurylidenemalonic acid by reduction with sodium amalgam.[20, 112] With urea and sodium ethoxide, the ester is converted into furfurylbarbituric acid, m.p. 186–187.5°[22] (see also Ojiyama *et al.*,[113] who give the m.p. as 193°).

α-Furfuryl-ethylmalonic acid: $C_4H_3O—CH_2—C(C_2H_5)(COOH)_2$; **diethyl ester,** b.p. 135.5–136.5° (5 mm.), prepared in 67 per cent yield by ethylation of preceding ester. Converted to furfuryl-ethylbarbituric acid, m.p. 144.5–145° in the usual manner.[22]

α-Furfuryl-2-cyclopentenylmalonic acid: $C_4H_3O—CH_2—C(C_5H_7)(COOH)_2$; **diethyl ester,** b.p. 116° (0.18 mm.); d_4^{25} 1.1018; n_D^{25} 1.4857. The ester was obtained from cyclopentenylmalonic ester and furfuryl chloride in the presence of sodium. Reduction gave rise to the corresponding furfuryl-cyclopentylmalonic ester, b.p. 107° (0.07 mm.); d_4^{25} 1.0925; n_D^{25} 1.4790.[43]

α-Furfuryl-2-cyclohexenylmalonic acid: diethyl ester, b.p. 124° (0.05 mm.), d_4^{25} 1.1035, n_D^{25} 1.4911.[43]

α-[(2-Furyl)(phenyl)methyl] malonic acid [2-(2-furyl)-2-phenyl-1,1-ethanedicarboxylic acid]: $C_4H_3O—CH(C_6H_5)—CH(COOH)_2$; m.p. 151°. **Diethyl ester,** b.p. 203° (14 mm.), obtained in 77 per cent yield by the action of PhMgBr on ethyl furfurylidenemalonate.[45] The ester was saponified and decarboxylated to obtain 3-(2-furyl)-3-phenylpropionic acid.[45]

α-[1-(2-Furyl)-*i*-pentyl]malonic acid [2-(2-furyl)-4-methyl-1,1-pentanedicarboxylic acid]; $C_4H_3O—CH(i\text{-}C_4H_9)—CH(COOH)_2$; **diethyl ester,** b.p. 153° (14 mm.), prepared in 71 per cent yield as in the preceding instance using *i*-BuMgCl. The ester was hydrolyzed to the corresponding acid (no constants) and decarboxylated to 3-(2-furyl)-5-methylcaproic acid.[45]

α-[1-(2-Furyl)-4-methyl-1-pentyl]malonic acid [2-(2-furyl)-5-methyl-1,1-hexanedicarboxylic acid]; $C_4H_3O—CH(i\text{-}C_5H_{11})—CH(COOH)_2$; **diethyl ester,** b.p. 165° (12 mm.), in 87 per cent yield as in preceding instance using *i*-AmMgBr. Ester saponified and the free dicarboxylic acid (no constants) decarboxylated with the formation of 3-(2-furyl)-6-methylheptanoic acid.[45]

2-Furylsuccinic acid: $C_4H_3O—CH(COOH)—CH_2COOH$; m.p. 154°; by saponification of the acid-nitrile, 3-(2-furyl)-3-cyanopropionic acid, derived from furfurylidenemalonic ester by the action of KCN. **Dimethyl ester,** b.p. 162–163° (30 mm.); **diethyl ester,** b.p. 199.5–200° (79 mm.); the **amido-acid,**

$$C_4H_3O—CH(CONH_2)—CH_2COOH$$

m.p. 155°, was obtained by hydrolysis of the corresponding cyano-acid; **diamide,** m.p. 220+° (dec.); the **dihydrazide,** m.p. 159–161°, condenses with benzaldehyde to give a **dibenzylidene derivative,** m.p. 199–200°. Heating the acid with aniline produced

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[112] Sandelin, *Ber.*, **33,** 489 (1900).

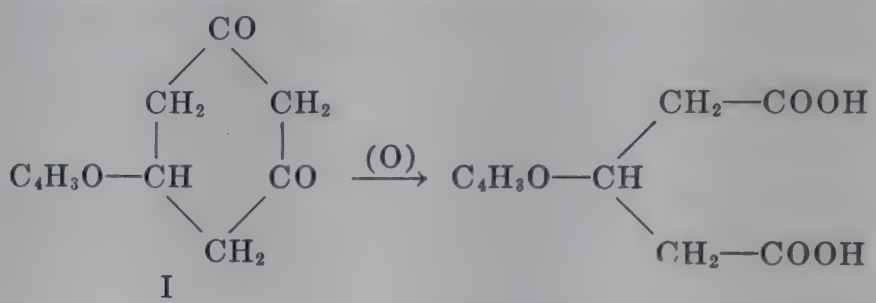
[113] Ojiyama, Hasegawa and Matsumura, *J. Pharm. Soc. Japan*, **533,** 597 (1926); *C. A.*, **21,** 2251 (1927).

a mono-anilide, m.p. 152.5°. On distillation, the free acid fails to give the anhydride, but loses carbon dioxide with the formation of 3-(2-furyl)propionic acid.[21, 111]

Furfurylsuccinic acid: $C_4H_3O—CH_2—CH(COOH)—CH_2COOH$; m.p. 139.5–140°, 141–142°; obtained by partial decarboxylation of 3-(2-furyl)-1,2,2-propanetricarboxylic acid,[111] and also by reduction of 2-furfurylidenesuccinic acid using sodium amalgam.[114] **Diethyl ester,** b.p. 213.5–215° (67 mm.).[111]

Difurfurylsuccinic acid: $C_4H_3O—CH_2—CH(COOH)—CH(CH_2—C_4H_3O)—COOH$; m.p. 173°, by reduction of difurfurylidenesuccinic acid with sodium amalgam.[114]

β-(2-Furyl)glutaric acid: m.p. 134–135, 138°, b.p. 180° (0.4 mm.), is obtained in 70 per cent yield by splitting furfurylidenebisacetoacetic ester with 60 per cent aqueous KOH,[115] and by partial decarboxylation of 2-(2-furyl-1,3,3-propanetricarboxylic acid.[116] It has also been synthesized by oxidative cleavage of 5-(2-furyl)-5,6-dihydroresorcinol (I; shown in keto form) using salts of hypohalous acids.[117]



I

Decarboxylation of the acid in β-naphthoquinoline in the presence of copper produce a small quantity of 2-*i*-propylfuran.[116]

3,4-Di(2-furyl)adipic acid: $C_4H_3O—CH(CH_2—COOH)—CH(C_4H_3O)—CH_2COOH$ Reduction of methyl 3-(2-furyl)acrylate using NH_4-Hg (3–16 amp. hr.) produced th expected furylpropionic ester, and in addition the **methyl ester** (m.p. 85°) of th above acid, and an oily product, which on saponification gave what is reported to b *iso*-β,β′-difuryladipic acid, m.p. 157–158°[118] (see also [119]).

Keto Dicarboxylic Acids and Their Derivatives

2-Furoylmalonic acid: the acid is unreported, but the **ethyl ester anilide,**

$$C_4H_3O—CO—CH(COOC_2H_5)—CONH(C_6H_5),$$

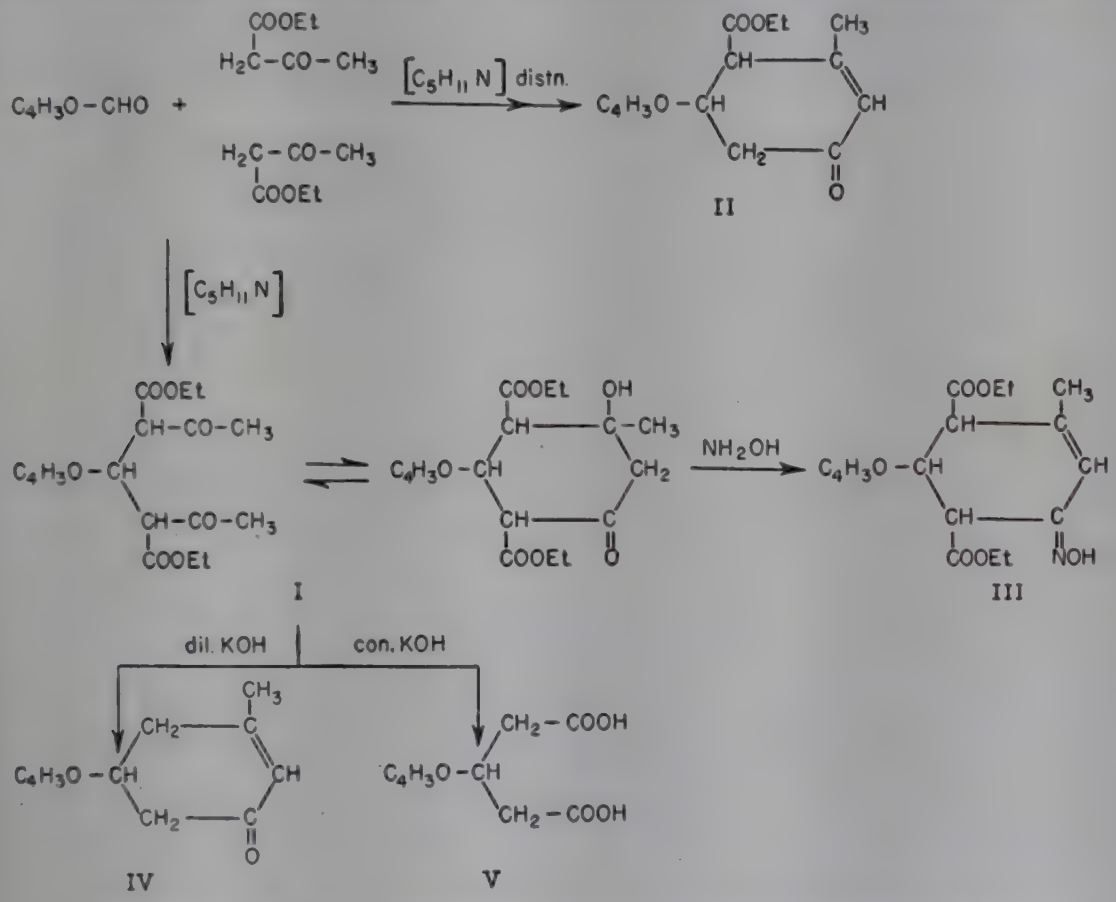
m.p. 144–146°, was obtained by condensation of phenyl isocyanate with ethyl s diofuroylacetate.[92]

Furyloxaloacetic acid: $C_4H_3O—CH(COOH)—CO—COOH$. Obtained as the **diethy ester** in 94 per cent yield by condensation of ethyl oxalate with furylacetic ester the presence of sodium ethoxide. The ester is not distillable, but loses carbon mon oxide on heating under vacuum to form furylmalonic ester.[6]

Furfurylidenebisacetoacetic ester: I (below); m.p. 72°; by condensation of furfur (1 mole) with acetoacetic ester (2 moles) under the influence of piperidine (1 g. The mixture solidified to a crystalline mass (I) after 48 hours. When this mass w allowed to stand for a longer time it became fluid again, following which removal the catalyst and distillation gave rise to 2-methyl-3-carbethoxy-4-(2-furyl)-1-cycl

[114] Fichter and Scheuermann, *Ber.*, **34,** 1626 (1901).
[115] Knoevenagel, *Ber.*, **35,** 392 (1902).
[116] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15,** 1118 (1932)
[117] Vorländer and Kohlmann, *Ann.*, **322,** 239 (1902).
[118] Takaki and Ueda, *J. Pharm. Soc. Japan*, **58,** 427 (1938); *C. A.*, **32,** 6636 (193
[119] Asahina and Shibata, *J. Pharm. Soc. Japan*, **423,** 391 (1917); *C. A.*, **11,** 2
(1917).

hexen-6-one, II, also melting at 72°. In other words, under these conditions, I loses the elements of water and one carbethoxy group is split off. I gives a violet-red color with ferric chloride in alcohol, whereas II produces no coloration under the same conditions. II forms an oxime, m.p. 110–112°. The oxime, III, derived from I melts at 142°, and the analytical data suggest that oximation was accompanied by formation of the cyclohexene ring. Attempts to split out water from I using hydrochloric acid to obtain the free methyldicarbethoxy-furylcyclohexenone were unsuccessful; resinous products were obtained which could not be crystallized. Hydrolytic cleavage of I proceeds normally, the ratio of "acid" to "ketone" splitting varying with the concentration of the reagent (see table below). With dilute alkali, the predominant product is 3-methyl-5-(2-furyl)-2-cyclohexenone, IV (b.p. 153–154° (10 mm.), d_4^{16} 1.1056, n_D^{16} 1.5354), whereas increasing alkali concentration produces more β-(2-furyl)glutaric acid, V, at the expense of the ketone. It will be observed that the "ketone" splitting is accompanied by dehydration to the cyclohexenone ring.[120, 115]



"Ketone" and "acid" splitting of furfurylidenebisacetoacetic ester

KOH concn. %	Product yield (%)	
	IV	V
6	quant.	—
10	64	5.7
40	45	51
43	32	60
60	17	70

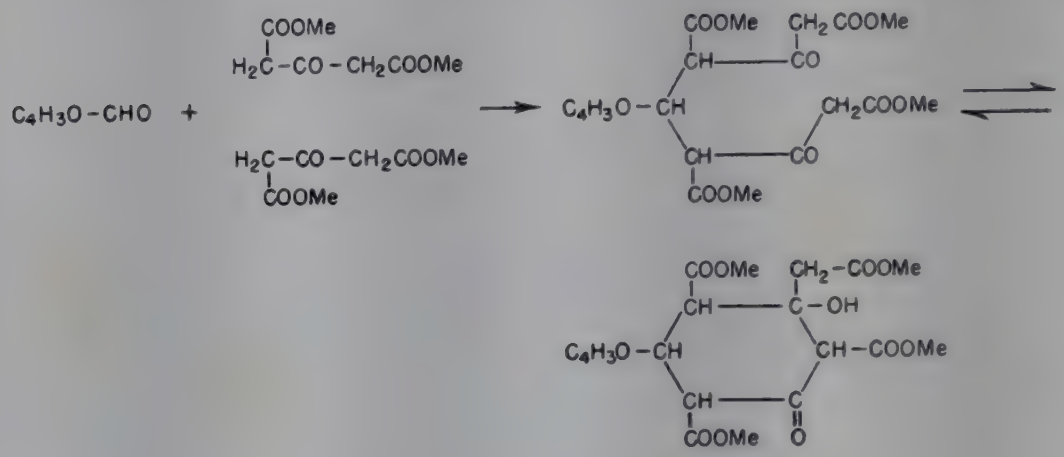
[120] Knoevenagel, *Ann.*, **303**, 223 (1898).

Miscellaneous Polycarboxylic Acids

2-(2-Furyl)-1,1,3-propanetricarboxylic acid: $C_4H_3O—CH(CH_2COOH)—CH(COOH)_2$; m.p. 58° (dec.); transition to β-(2-furyl)glutaric acid. The **triethyl ester,** b.p. 162–165° (0.7 mm.), was obtained in 49 per cent yield by the addition of malonic ester to the olefinic double bond of ethyl 3-(2-furyl)acrylate under the influence of sodium ethoxide.[116]

3-(2-Furyl)-1,2,2-propanetricarboxylic acid: $C_4H_3O—CH_2—C(COOH)_2—CH_2COOH$; m.p. 155–156°; by saponification of the **triethyl ester,** b.p. 212–213.5° (25 mm.), derived in 40 per cent yield by condensation of furfurylmalonic ester with chloroacetic ester, by means of sodium ethoxide.[112]

Furfurylidenebis-β-ketoglutaric methyl ester: m.p. 162–175° (dec). This product has been reported as one product of the condensation of furfural with methyl β-ketoglutarate (methyl acetonedicarboxylate) using either ammonia or diethylamine as the condensing agent. It had been anticipated that, using ammonia, a γ-piperidone derivative would be formed (as in the case of benzaldehyde). From the mother liquor an oily compound containing nitrogen was obtained, but it was not characterized.[121]



Furylalkenoic Acids

Within the scope of this section are the furancarboxylic acids in which one or more carboxyl groups are attached to a side chain possessing one or more olefinic linkages. Such acids can be obtained by oxidation of the corresponding aldehydes, but have been synthesized more frequently by the general procedures available for compounds of this type, such as the Perkin and Claisen methods.

The Perkin reaction was first applied to a furan aldehyde by Baeyer in 1877.[17] By condensing furfural with sodium acetate in acetic anhydride he successfully prepared 3-(2-furyl)acrylic acid, the simplest member of the class of compounds under discussion. With butyric anhydride[d] and sodium butyrate, furfural yields the expected disubstituted acrylic acid, $C_4H_3O—CH=C(C_2H_5)—COOH$ (furylangelic acid) in high yield.[27] Simi-

[d] Substitution of acetic anhydride for butyric anhydride in this reaction results in the formation of 3-(2-furyl)acrylic acid as the major product.[27]

[121] Petrenko-Kritschenko and Lewin, *Ber.*, **40**, 2882 (1907).

larly, the corresponding phenyl substituted acid is derived from furfural and sodium phenylacetate in acetic anhydride.[122, 123]

$$C_4H_3O{-}CHO + (RCH_2CO)_2O \xrightarrow{RCH_2COONa} C_4H_3O{-}CH{=}CR{-}COOH$$

The use of isovaleric anhydride and its sodium salt in the Perkin reaction with furfural gives only a very small yield of the expected acrylic acid derivative. Even at a temperature as low as 70°, carbon dioxide is evolved, and the major product is 2-(2-*i*-propylvinyl)furan.[124] The lower homolog, 2-(2,2-dimethylvinyl)furan, I, is the product of condensation of furfural with isobutyric anhydride and sodium isobutyrate at 100°.[56] By analogy with the corresponding reaction with benzaldehyde, it may be assumed that 2,2-dimethyl-3-*i*-butyroxy-3-furylpropionic acid, A, is formed as an intermediate, and that A undergoes decarboxylation more readily than the related phenylpropionic acid.[125, 126]

$$C_4H_3O{-}CHO \xrightarrow[i{-}C_3H_7COONa]{(i{-}C_3H_7CO)_2O}$$

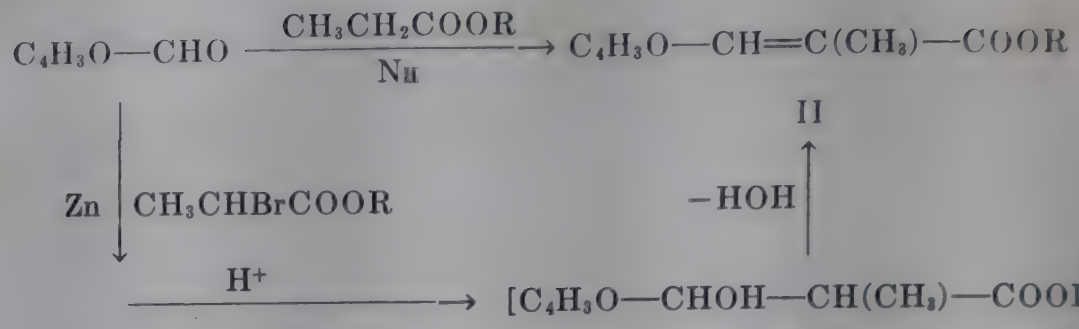
$$C_4H_3O{-}\underset{\displaystyle O{-}COC_3H_7}{\underset{|}{CH}}{-}C(CH_3)_2{-}COOH \xrightarrow[-C_3H_7COOH]{-CO_2} \underset{\displaystyle I}{C_4H_3O{-}CH{=}C(CH_3)_2}$$

(A)

The Perkin synthesis has also been applied to 5-methylfurfural[12, 38, 127, 128] and to 5-(hydroxymethyl)furfural[129] with formation of the appropriate nuclear substituted furylacrylic acids. For furylacrolein in the Perkin reaction, see Röhmer.[122]

Furylalkenoic esters are obtainable by means of the Claisen synthesis, and these, of course, may be saponified if it is desired to obtain the free carboxylic acids. Application of furfural in this synthesis was first carried out by Claisen himself; furfural and ethyl acetate in the presence of sodium gave rise to ethyl 3-(2-furyl)acrylate.[130] Substitution of esters of higher fatty acids for ethyl acetate produces furylacrylic esters alkylated in the side chain. Thus, furfural and propionic ester give 3-(2-furyl)-2-methylacrylic ester, II,[131] which is also formed by reaction of furfural with 2-bromopropionic ester according to the Reformatsky procedure.[132]

[122] Röhmer, *Ber.*, **31**, 281 (1898).
[123] Maxim and Stancovici, *Bull. soc. chim.* (*5*), **2**, 600 (1935).
[124] Schaarschmidt, Georgeacopol and Herzenberg, *Ber.*, **51**, 1059 (1918).
[125] Fittig, *Ann.*, **227**, 48 (1885).
[126] Hauser and Breslow, *J. Am. Chem. Soc.*, **61**, 793 (1939).
[127] Maquenne, *Compt. rend.*, **109**, 571 (1889).
[128] Maquenne, *Ann. chim. phys.* (*6*), **22**, 76 (1891).
[129] Karashima, *Z. physiol. Chem.*, **180**, 241 (1929); *C. A.*, **23**, 2175 (1929).
[130] Claisen, *Ber.*, **24**, 143 (1891).
[131] Kasiwagi, *Bull. Chem. Soc. Japan*, **2**, 310 (1927); *C. A.*, **22**, 778 (1927).
[132] Buu-Hoi, Cagniant, Janicaud and Finiger, *Bull. soc. chim.*, **10**, 137 (1943).



Furan aldehydes likewise condense in the normal fashion with malonic acid and ester,[e] cyanoacetic ester and aliphatic keto esters under appropriate conditions to give furylalkenecarboxylic acids and esters. For convenience these are considered later under the appropriate product classification.

TABLE 3. PERKIN SYNTHESIS OF 3-(2-FURYL)ACRYLIC ACID

$$C_4H_2O—CHO + (CH_3CO)_2O \xrightarrow{AcONa} C_4H_3O—CH=CH—COOH$$

Molar ratio of reactants			Conditions		Yield (%)	Ref.
furfural	Ac_2O	AcONa	time (hrs.)	temp. (°C.)		
1.0	3.8	2.3	8	reflux	—	17
1.0	3.8	2.3	8	reflux	70	18; see also 134
1.0	1.9	2.3	11	150	80	18
1.0	1.9	2.3	11	170	88–90	135
1.0	1.9	2.3	6–8	146–147	73–84*	136
1.0	1.4	1.8	10	160–170	70	137
1.0	1.4	1.8	9	160–165	66	140
1.0	1.4	1.8	10	165–170	80	141
1.0	1.25	1.0 (AcOK)	4	150	65–70	138

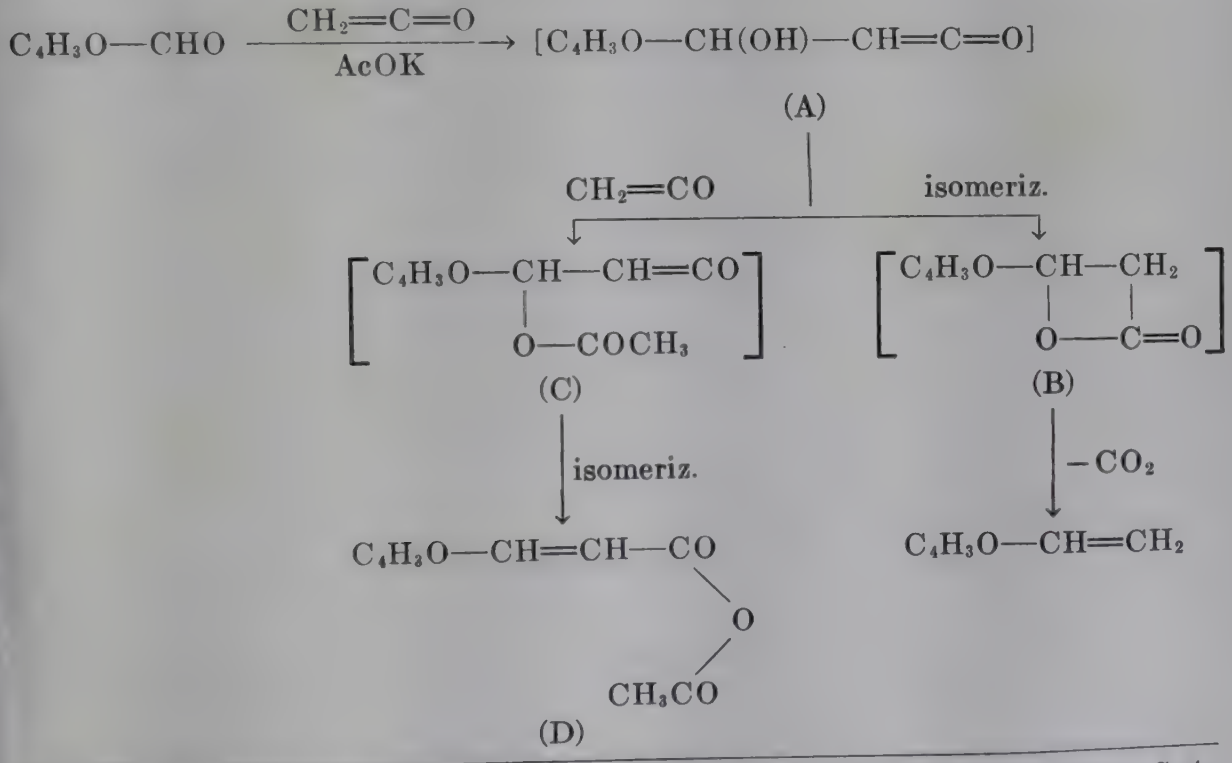
* The commercial grade of furfural was employed in this work, and it should be observed that Gilman's product (m.p. 138°) is sufficiently pure, for most purposes, without the necessity for recrystallization.[136] In his hands, the use of a reduced ratio of acetic anhydride to furfural (as employed by Gibson and Kahnweiler[137]) yielded a considerably more impure product (m.p. 130°). Isolation of the acid involved dilution of the reaction mixture with water, steam distillation, and treatment of the residual liquor with carbon prior to crystallization from water. The method of recovery employed by Johnson[138] is similar, but omits the time-consuming steam distillation. Despite this, and the lower ratio of acetic anhydride to furfural used by Johnson, the product obtained is of a purity comparable to that of Gilman, although the yield is somewhat lower. One of the advantages of Gilman's procedure is the use of the commercial grade of furfural rather than a freshly distilled product. Kalnin[139] studied the effect of catalysts on the reaction. He found salts, such as carbonates, to be effective; that tertiary amines may be substituted for salt. Gilman[136] checked the influence of pyridine as a catalyst with inconclusive results.

[e] An exception is noted in the case of 5-(bromomethyl)furfural (see [86]).

3-(2-Furyl)acrylic Acid and Related Acids

Since Baeyer first accomplished the preparation of 3-(2-furyl)acrylic acid by the Perkin reaction, several modifications of his procedure have been tested with the results listed in Table 3. Additionally, attention is called to a patented modification[133] in which furfural and acetic anhydride are condensed in the vapor phase over a catalyst comprising sodium acetate and silica gel.

A modified Perkin reaction, in which ketene is substituted for acetic anhydride, has been described by Hurd and Thomas[142] (see also [143, 144]). In the presence of a little potassium acetate, ketene reacts exothermically with furfural to give as the chief product, the mixed anhydride of acetic and 3-(2-furyl)acrylic acids. The reaction is considered to proceed by way of the substituted ketene, A, which rearranges in part to β-2-furyl-β-propionolactone, B, but which for the most part reacts further with ketene to the ketene ester, C, and this undergoes rearrangement to the mixed anhydride, D. The yield of furylacrylic acid obtained by hydrolysis of D (which was not isolated) was 43.5 per cent of the theoretical quantity based on the furfural used.



[133] Brubaker (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,341,016 (1944); *C. A.*, **38**, 4272 (1944).

[134] Jaffe and Cohn, *Ber.*, **20**, 2311 (1887).

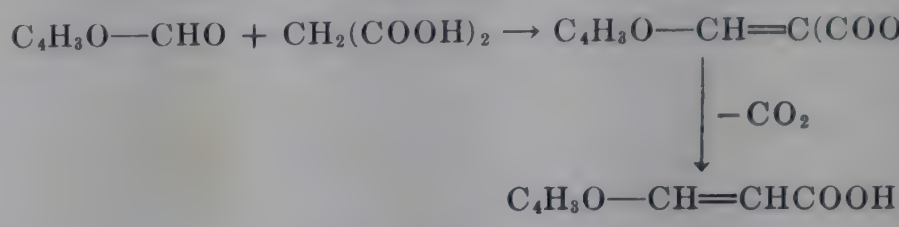
[135] Koton, Votinova and Florinskii, *J. Applied Chem. U.S.S.R.*, **14**, 181 (1941); *C. A.*, **36**, 1604 (1942).

[136] Gilman, Brown, Wright and Hewlett, *Iowa State Coll. J. Sci.*, **4**, 355 (1930).

[137] Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).

[138] Johnson, "Organic Syntheses," Vol. 20, p. 55, New York, John Wiley and Sons, Inc. (1940).

Another procedure which has found favor for the laboratory preparation of furylacrylic acid is the reaction of furfural with malonic acid under the condensing influence of pyridine or piperidine. Condensation leads to the formation of furfurylidenemalonic acid which, under appropriate experimental conditions, readily loses carbon dioxide with formation of the de-



sired product. The early work of Marckwald,[145] Liebermann,[146] Knoevenagel[147] and Sandelin[112] has been modified by later investigators,[148, 113, 149, 150, 151, 152] and it is now possible to prepare furylacrylic acid in excess of 90 per cent yield by this procedure.[153]

Yet another method of preparative value, and probably that most attractive from a commercial standpoint, involves the oxidation of furfurylideneacetone with alkaline hypochlorite. Furylacrylic acid was first obtained in this manner by Schmidt,[154] and the method is the subject of a patent to Yabuta.[155] Yabuta and Kambe[156] and Hurd and Thomas[157] employed commercial bleaching powder as the oxidizing agent, the latter investigators reporting a yield of 89.5 per cent based on the furfurylideneacetone (see also [131]). A recently patented process for the synthesis of the

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[139] Kalnin, *Helv. Chim. Acta*, **11**, 977 (1928).

[140] Moureu, Dufraisse and Johnson, *Ann. chim.* (*10*), **7**, 13 (1927).

[141] Galimberti, *Boll. sci. facoltà chim. ind. Bologna*, **1940**, 351; *C. A.*, **37**, 3410 (1943).

[142] Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 275 (1933).

[143] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,466,420 (1949); *C. A.*, **43**, 5037 (1949).

[144] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,484,499 (1949).

[145] Marckwald, *Ber.*, **21**, 1398 (1888).

[146] Liebermann, *Ber.*, **27**, 283 (1894).

[147] Knoevenagel, *Ber.*, **31**, 2596 (1898).

[148] Dutt, *Quart. J. Indian Chem. Soc.*, **1**, 297 (1925); *C. A.*, **19**, 2475 (1925).

[149] Kurien, Pandya and Surange, *J. Indian Chem. Soc.*, **11**, 823 (1934); *C. A.*, **29**, 3325 (1935).

[150] Faber, *Seifenseider-Ztg.*, **66**, 534, 554, 574 (1939); *C. A.*, **33**, 7487 (1939).

[151] Mittal, *J. Indian Chem. Soc.*, **19**, 47 (1942); *C. A.*, **36**, 5469 (1942); *Ibid.*, **21**, 34 (1944); *C. A.*, **39**, 285 (1945).

[152] Rajagopalan, *Proc. Indian Acad. Sci.*, **16, A**, 163 (1942); *C. A.*, **37**, 1423 (1943).

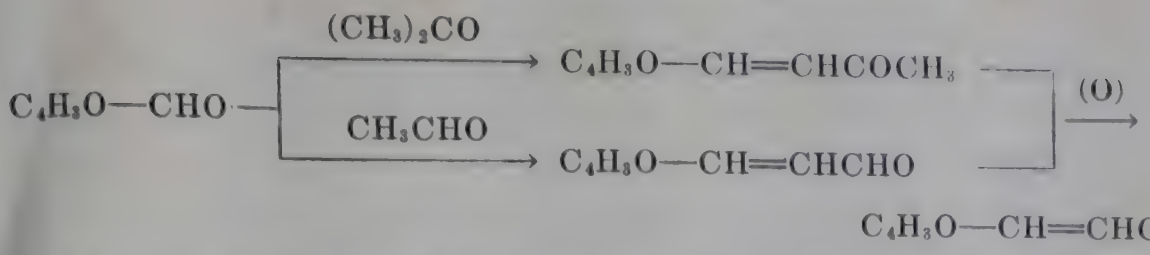
[153] Rajagopalan and Raman, "Organic Syntheses," Vol. 25, p. 51, New York, John Wiley and Sons, Inc. (1945).

[154] Schmidt, *Ber.*, **14**, 1459 (1881).

[155] Yabuta (to S. Furukawa), Japanese Pat. 71,065 (1926).

[156] Yabuta and Kambe, *Proc. Imp. Acad. Tokyo*, **4**, 120 (1928); *C. A.*, **22**, 4503 (1928).

[157] Hurd and Thomas, *J. Am. Chem. Soc.*, **55**, 1646 (1933).



acid involves oxidation of the corresponding aldehyde, 3-(2-furyl)acrolein, in the liquid phase using air in the presence of colloidal silver.[158]

Claisen's[130] preparation of ethyl furylacrylate by the synthesis which bears his name resulted in a 36 per cent yield. A considerable improvement has been achieved in later work[159] (see also [150]), the highest reported yield being 80 per cent.[6] Higher esters of furylacrylic acid are obtained by employing an acetic ester possessing the desired alcohol residue.[160, 161]

As an ethylenic derivative, 3-(2-furyl)acrylic acid exists in *cis* and *trans* stereoisomeric forms. The ordinary or *trans* form, as obtained in the Perkin synthesis, melts at 141° when pure. The *cis* isomer (Liebermann's *allo*-furylacrylic acid[f]) apparently exists in polymorphic modifications, m.p. 103–104°,[162, 163] and m.p. 113°.[164] It is obtained, in admixture with the more stable *trans* form by decarboxylation of furfurylidenemalonic acid, and is slowly converted into the *trans* form by heat[162] or by exposure to direct sunlight.[164] In the latter instance, the presence of a trace of iodine greatly accelerates the rate of transformation.[164]

Ordinary furylacrylic acid is only slightly soluble in cold water, more easily in hot water, alcohol and benzene. It is reported to sublime at 112° in high vacuum[165] and to boil at 226°.[18] At 250–300° it undergoes decarboxylation with the formation of 2-vinylfuran[140] (see also p. 73). For thermochemical data, see Landrieu, Baylocq and Johnson.[166]

The effect of the ethylenic linkage in decreasing the reactivity of the carboxyl group in furylacrylic acid and other substituted acrylic acids was investigated by Sudborough.[163, 19] By studying the rates of esterification (k) under comparable conditions he obtained the following results.

[f] Earlier, Liebermann[146] isolated an impure product, melting over the range 82–87°, which he regarded as the *allo* acid. Subsequently, this was shown to be a mixture of the *cis* and *trans* isomerides, separable by way of their piperidine salts.[162]

[158] Gavatin (to Mo Och Domsjö Aktiebolag), Swedish Pat. 118,461 (1947); *C. A.*, **42**, 223 (1948).

[159] Gilman, Brown and Jones, *Iowa State Coll. J. Sci.*, **2**, 317 (1928).

[160] Wienhaus and Leonhardi, *Ber. Schimmel & Co., Akt.-Ges.*, **1929**, 225; *C. A.*, **24**, 2127 (1930).

[161] Blumann and Hesse, *Perfumery and Essent. Oil Record*, **22**, 382 (1931); *C. A.*, **26**, 3792 (1932).

[162] Liebermann, *Ber.*, **28**, 129 (1895).

[163] Sudborough and Roberts, *J. Chem. Soc.*, **87**, 1840 (1905).

[164] Liebermann, *Ber.*, **28**, 1443 (1895).

[165] Liebermann and Riiber, *Ber.*, **33**, 2400 (1900).

[166] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).

	k		k
C_4H_3O—CH=CHCOOH	0.72	C_4H_3O—CH_2CH_2COOH	43.9
C_6H_5CH=CHCOOH	0.94	$C_6H_5CH_2CH_2COOH$	47.3

Derivatives of furylacrylic acid:

Esters: these may be obtained by the Claisen condensation of furfural with acetic esters, or from furylacrylyl chloride and the appropriate alcohol in benzene. Using the latter method in the presence of an excess of pyridine, Bartlett and Ross[167] have recently reported excellent yields of a variety of the esters. It is interesting to observe that allyl furylacrylate was one of the first of the allyl esters employed to obtain a thermosetting resin.[168, 169] Attempted esterification with alcohol and hydrogen chloride in the usual manner proceeds largely with nuclear cleavage and formation of esters of ketopimelic acid (see p. 626). The known esters are listed in Table 4.

Furylacrylyl chloride, b.p. 106.5° (6 mm.), 126° (30 mm.); prepared in 90 per cent yield by the action of thionyl chloride on the acid benzene[170] (see also [35, 171, 172, 132, 167]). Treatment with sodium peroxide yields **difurylacrylyl peroxide,** m.p. 104° (dec.) which explodes violently on application of heat.[173] For use of the acid chloride in the Friedel-Crafts reaction, see Maxim and Popesco.[174] With hydroxylamine, the chloride is converted into **furylacrylohydroxamic acid,** C_4H_3O—CH=CH—CONHOH, m.p. 137–138° (dec.).[175] **Furylacrylamide,** m.p. 168–169°.[172, 176] **Amido derivatives:** N-*i*-pentyl, m.p. 60–61°, b.p. 197–198° (5.5 mm.)[177]; N-benzyl, m.p. 145–146°[178]; N,N-diethyl, b.p. 186° (15 mm.)[44]; N-methyl-N-phenyl, m.p. 117.5°[44]; N-ethyl-N-phenyl, m.p. 60°[44]; N,N-diphenyl, m.p. 181.5°, 186–187°[44, 179]; ureide, m.p. 204–206°[176]; homoveratrylamide, m.p. 108–109°[180]; N-furylacrylylglycine, C_4H_3O—CH=CH—NH-(CH_2COOH), m.p. 218–219°.[35] **Furylacrylonitrile,** C_4H_3O—CH=CHCN, m.p. 38°, b.p. 86–91° (10 mm.) is obtained directly by catalytic condensation of furfural with acetonitrile in the vapor phase at 320°.[133] Prior to this patented method, the nitrile had been synthesized by (1) dehydration of the corresponding amide over phosphorus pentachloride[172] and (2) by decarboxylation of 3-(2-furyl)-2-cyanoacrylic acid.[181]

Related furylacrylic acids and their derivatives:

3-(2-Furyl)-2-methylacrylic acid: C_4H_3O—CH=C(CH_3)—COOH; m.p. 110.5–111°, obtained by condensation of furfural with propionic ester and subsequent hydrolysis[131]; by oxidation of α-furfurylidenepropionaldehyde[183]; by oxidation of 4-(2-furyl)-3-methyl-3-buten-2-one, C_4H_3O—CH=C(CH_3)—$COCH_3$, with sodium hypochlo-

[167] Bartlett and Ross, *J. Am. chem. Soc.*, **69**, 460 (1947).
[168] Blicke, *Ber.*, **47**, 1352 (1914).
[169] Blicke, *J. Am. Chem. Soc.*, **45**, 1562 (1923).
[170] Gilman and Wright, *Iowa State Coll. J. Sci.*, **3**, 109 (1928).
[170a] The Quaker Oats Co., unpublished data.
[171] Gilman and Pickens, *J. Am. Chem. Soc.*, **47**, 245 (1925).
[172] Gilman and Hewlett, *Iowa State Coll. J. Sci.*, **4**, 27 (1929).
[173] Milas and McAlevy, *J. Am. Chem. Soc.*, **56**, 1219 (1934).
[174] Maxim and Popesco, *Bul. soc. chim. Romania*, **16**, 89 (1934); *C. A.*, **29**, 4355 (1935).
[175] Gilman and Yale, *J. Am. Chem. Soc.*, **72**, 3593 (1950).
[176] Lott and Christiansen, *J. Am. Pharm. Assoc.*, **23**, 788 (1934).
[177] Kaneo and Inakawa, *J. Pharm. Soc. Japan*, **58**, 261 (1938); *C. A.*, **32**, 4141 (1938).
[178] Dermer and King, *J. Org. Chem.*, **8**, 168 (1943).
[179] Chelintzev and Benevolenskaya, *J. Gen. Chem. U.S.S.R.*, **7**, 2361 (1937); *C. A.*, **32**, 2123 (1938).

TABLE 4. SOME ESTERS OF 3-(2-FURYL)ACRYLIC ACID

$C_4H_3O—CH=CH—COOR$

Ester	Physical constants (°C.)	Ref.
Methyl	m.p. 27, 27.5; b.p. 114–115 (16 mm.), 89 (5 mm.); n_D^{20} 1.4447	170, 161, 133
Ethyl	m.p. 24.5; b.p. 233–235 (−), 120–121 (17 mm.), 118–119 (10 mm.); d_4^{26} 1.0891; n_D^{20} 1.5286, 1.5461	130, 161, 159 170, 32, 6, 170a
2-Methoxyethyl	m.p. 33–34; b.p. 118–120 (3 mm.)	167
2-Ethoxyethyl	b.p. 124–126 (3 mm.); n_D^{25} 1.5398	167
2-Chloroethyl	b.p. 130–132 (4 mm.)	182
2-Diethylaminoethyl	**hydrochloride,** m.p. 137–138	171
n-Propyl	b.p. 91–94 (3 mm.); n_D^{24} 1.5392 d_4^{20} 1.0744	170, 167
i-Propyl	b.p. 98 (4.5 mm.); n_D^{20} 1.5146; d_4^{20} 1.0503	170
Allyl	b.p. 131–133 (16 mm.); n_D^{25} 1.5573	167, 168
Methallyl	b.p. 93.5–94 (3 mm.); n_D^{25} 1.5500	167
n-Butyl	b.p. 117–118 (3 mm.); n_D^{20} 1.5129 d_{20} 1.045	170, 160
i-Butyl	b.p. 94–95 (2 mm.); n_D^{24} 1.5277	167
n-Pentyl	b.p. 116.5–118 (2 mm.); n_D^{24} 1.5289 d_4^{20} 1.0322	167, 170
i-Pentyl	b.p. 123–124 (5 mm.); 136–139 (5 mm.) n_D^{25} 1.5253; n_D^{20} 1.5244; d_{20} 1.025	167, 160
2-Ethylbutyl	b.p. 119–120 (3 mm.); n_D^{25} 1.5239	167
Cyclohexyl	m.p. 52–53; b.p. 121–124 (3 mm.)	167
Benzyl	m.p. 42–43; b.p. 131–132 (3 mm.)	167, 170, 171
2-Phenethyl	b.p. 155–156 (3 mm.); n_D^{25} 1.5872	167
Phenyl	b.p. 185 (4 mm.)	182
m-Tolyl	b.p. 185 (5 mm.); d_4^{35} 1.0728 n_D^{34} 1.5980	182
p-Tolyl	m.p. 75; b.p. 195 (6 mm.)	182
o-Hydroxyphenyl (catechol monoester)	m.p. 132	182
o-Methoxyphenyl (guaiacol ester)	m.p. 105; b.p. 210 (6 mm.)	182
m-Hydroxyphenyl (resorcinol monoester)	m.p. 128	182
m-Phenylene (resorcinol diester)	m.p. 112	182
p-Hydroxyphenyl (hydroquinone monoester)	m.p. 173	170
Furfuryl	m.p. 52	

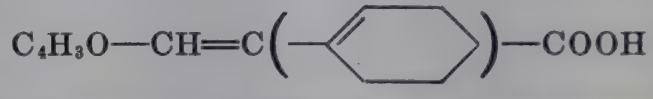
[180] Harwood and Johnson, *J. Am. Chem. Soc.*, **55**, 2555 (1933).
[181] Heuck, *Ber.*, **27**, 2624 (1894).
[182] Gilman, Heckert, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **7**, 419 (1933).
[183] Schmidt, *Ber.*, **14**, 574 (1881).

rite,[131] and from furfural and 2-bromopropionic acid according to the method of Reformatsky.[132] **Esters:** ethyl, b.p. 103–104° (4.5 mm.), d_4^{25} 1.0800, n_D^{25} 1.5418; dihydrohydnochaulyl (a name which according to the nomenclature of Wagner-Jauregg designates a mixture of dihydrohydnocarpyl and dihydrochaulmoogryl alcohols), b.p. 225–230° (0.2 mm.). **Acid chloride,** b.p. 127° (12 mm.). **Amide,** m.p. 137°.

3-(2-Furyl)-2-ethylacrylic acid (furylangelic acid): $C_4H_3O—CH=C(C_2H_5)—COOH$; m.p. 95.5–97°, by Perkin reaction from furfural, butyric anhydride and sodium butyrate.[27] (Earlier, Baeyer, and Tonnies[56, 55] formulated the product incorrectly as $C_4H_3O—CH=CH—CH_2CH_2COOH$). Oxidation with alkaline permanganate produced furoic acid and smaller amounts of acetic and propionic acids. With the same reagent in acidic medium a considerable amount of carbon dioxide was evolved. Acetic and propionic acids were identified in the reaction mixture, but no furoic acid was found. It was postulated that the former two have their origin in some intermediate oxidation product, probably ketobutyric acid.[27]

3-(2-Furyl)-2-*i*-propylacrylic acid: $C_4H_3O—CH=C(i\text{-}C_3H_7)—COOH$; m.p. 114°, in very poor yield from furfural, *i*-valeric anhydride and sodium *i*-valerate. The major product is 2-(3-methyl-1-butenyl)furan due to decarboxylation at some stage during the reaction.[124]

3-(2-Furyl)-2-(1-cyclohexenyl)acrylic acid:



m.p. 151.5–152°, by condensation of furfural with 1-cyclohexenylacetic acid in the presence of triethylamine.[184]

3-(2-Furyl)-2-phenylacrylic acid: $C_4H_3O—CH=C(C_6H_5)—COOH$; m.p. 143–144°, by the Perkin reaction using furfural, sodium phenylacetate and acetic anhydride.[122, 123] **Esters:** methyl, m.p. 88°; ethyl, m.p. 54°; propyl, b.p. 187° (17 mm.); butyl, b.p. 204° (17 mm.); pentyl, b.p. 210° (17 mm.). The diethylaminoethyl ester, m.p. 157°, was tested as an antispasmodic by Burtner and Cusic.[185] **Acid chloride,** m.p. 43°; b.p. 183° (15 mm.). **Amide,** m.p. 127°. **Substituted amides:** anilide, m.p. 104°; piperidide, m.p. 105°; N-dimethyl, b.p. 205° (16 mm.); N-diethyl, b.p. 211° (17 mm.); N-methyl-N-phenyl, b.p. 234° (17 mm.); N-ethyl-N-phenyl, b.p. 236° (18 mm.); N-diphenyl, m.p. 108°, b.p. 272° (12 mm.). **Nitrile,** m.p. 42–43°, obtained directly by condensing furfural with benzyl cyanide in the presence of sodium ethoxide.[186, 187, 188] The related nitriles listed below were similarly obtained from furfural and the appropriately substituted benzyl cyanide, and from furfural and 2-thienylacetonitrile:

$$C_4H_3O—CH=CR—CN$$

where R = *m*-methoxyphenyl, b.p. 180° (1 mm.)[186]
p-chlorophenyl, m.p. 80°[189]
p-bromophenyl, m.p. 65°[188]
p-aminophenyl, m.p. 111–112°[187]
p-diacetamidophenyl, m.p. 203–204°[187]
p-nitrophenyl, m.p. 171–173°[187]
p-(phenylureido)phenyl, m.p. 159–160°[187]
p-(ω-allylthioureido)phenyl, m.p. 206–208°[187]
p-cyclohexylphenyl, m.p. 64°[190]
2-thienyl, m.p. 79°[191]

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[184] Schwenk and Papa, *J. Am. Chem. Soc.*, **67**, 1432 (1945).
[185] Burtner and Cusic, *J. Am. Chem. Soc.*, **65**, 262 (1943).

3-(2-Furyl)-2-chloroacrylic acid: $C_4H_3O—CH=CCl—COOH$; m.p. 142°, by condensation of furfural with chloroacetaldehyde and oxidation of the resulting 3-(2-furyl)-2-chloroacrolein with silver oxide.[192]

3-(5-Methyl-2-furyl)acrylic acid: $CH_3—C_4H_2O—CH=CHCOOH$; m.p. 153–154°, 157°, by the Perkin reaction using 5-methylfurfural and a mixture of acetic anhydride and sodium acetate.[127, 128, 12, 38] Also by decarboxylation of the intermediate dicarboxylic acid resulting from condensation of 5-methylfurfural with malonic acid in pyridine[193] (see also [194, 16, 195]). **Acid chloride:** m.p. 37°; b.p. 124° (9 mm.).[193] **Amide:** m.p. 130°. When fed to rabbits, the amide is eliminated in the urine in the form of the oxidation product, 3-(5-carboxy-2-furyl)acrylamide, m.p. 280°.[193]

3-(5-Hydroxymethyl-2-furyl)acrylic acid: $HOCH_2—C_4H_2O—CH=CHCOOH$; m.p. 139°; by hydrolysis of the acetoxymethylfurylacrylic acid, m.p. 134°, derived from 5-(hydroxymethyl)furfural, acetic anhydride and sodium acetate in the Perkin reaction.[129] Animal metabolism (dog) converts (acetoxymethyl)furylacrylic acid to 3-(5-carboxy-2-furyl)acrylic acid, m.p. 277°, which may be isolated from the urine.[196] 5-(2-Carboxyvinyl)-2-furfuryl ether, $(HOOCCH=CH—C_4H_2O—CH_2)_2O$, m.p. 203–204°, was obtained by Aso[197] by the action of sodium acetate and acetic anhydride on 5-(oxydimethylene)difurfural (see also [80]).

Like the related cinnamic acid and its homologs, the α,β-unsaturated furylalkenoic acids and their derivatives participate in a variety of addition reactions. Thus, they may be hydrogenated catalytically, or reduced by use of sodium amalgam to the appropriate alkanoic acids. Under certain conditions, coupling may occur during reduction to give bimolecular products, as in the reported isolation of 3,4-difuryladipic ester, I, as a product of the action of ammonium amalgam on methyl furylacrylate.[118]

$$C_4H_3O—CH=CH—COOR \xrightarrow[NH_4—Hg]{2H} \underset{\text{(3–16 amp. hr.)}}{}$$

$$C_4H_3O—CHCH_2COOR$$
$$|$$
$$C_4H_3O—CHCH_2COOR + C_4H_3O—CH_2CH_2COOR$$
$$\text{I}$$

[188] Woodward, *J. Am. Chem. Soc.*, **62**, 1478 (1940).
[187] Freund and Immerwahr, *Ber.*, **23**, 2845 (1890).
[188] Frost, *Ann.*, **250**, 156 (1889).
[189] Walther and Wetzlich, *J. prakt. Chem.*, **61**, 169 (1900).
[190] Buu-Hoi, Cagniant and Mentzner, *Bull. soc. chim.*, **11**, 127 (1944).
[191] Cagniant and Cagniant, *Compt. rend.*, **229**, 1150 (1949).
[192] Mehne, *Ber.*, **21**, 423 (1888).
[193] Kühn, Köhler and Köhler, *Z. physiol. Chem.*, **247**, 197 (1937); *C. A.*, **31**, 6264 (1937).
[194] Rothrock (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,381,881 (1945); *C. A.*, **39**, 5094 (1945).
[195] Wagner (to Phillips Petroleum Co.), U. S. Pat. 2,431,216 (1947); *C. A.*, **42**, 1609 (1948).
[196] Karashima, *Z. physiol. Chem.*, **184**, 265 (1929); *C. A.*, **24**, 362 (1930).
[197] Aso, *J. Agr. Chem. Soc. Japan*, **15**, 56 (1939); *C. A.*, **33**, 4984 (1939).

Under the influence of sodium ethoxide, malonic ester adds to furylacrylic ester with formation of 2-(2-furyl)-1,1,3-propanetricarboxylic ester, II, in 49 per cent yield.[116]

$$C_4H_3O{-}CH{=}CH{-}COOR + CH_2(COOR)_2 \xrightarrow{NaOEt} C_4H_3O{-}CH(CH_2COOR){-}CH(COOR)_2$$

II

The Grignard reagent likewise adds to these furylalkenoic acids (or derivatives such as the esters, amides and nitriles). Depending upon experimental conditions, addition to the side chain may occur by a 1,4- or 1,2-mechanism or by a combination of these. For example, Maxim and his coworkers[44, 46, 48] synthesized a variety of β,β-disubstituted propionic acids and related types according to the equation illustrated below. These reactions proceed by 1,4- addition and subsequent rearrangement leading to saturation of the α,β-double bond. As expected, when the ester is employed

$$C_4H_3O{-}CH{=}CH{-}\left\{\begin{matrix}COOR'\\CONR_2\\CN\end{matrix}\right. \xrightarrow{RMgX} \xrightarrow{HX} C_4H_3O{-}CHR{-}CH_2{-}\left\{\begin{matrix}COOR'\\CONR_2\\CN\end{matrix}\right.$$

as the starting material there is formed, as an additional product, the appropriate tertiary alcohol, $C_4H_3O{-}CH{=}CH{-}CR_2OH$ (see p. 263); here the attack of the organomagnesium halide is confined to the ester carbonyl group (1,2-addition).[48, 46]

Hydroxylamine adds very slowly to furylacrylic acid on heating (more rapidly to the ester) to give a complex mixture of products as a result of secondary condensations and oxidation-reduction. From the mixture, Posner[82, 81] was able to isolate the β-hydroxylamino acid, III, the β-amino acid, IV, 3-furyl-5-isoxazolone, V, and the oxime, VI. A similar result was obtained by reacting furfurylidenehippuric acid with hydroxylamine.[81]

$$C_4H_3O{-}CH{=}CHCOOH \xrightarrow[240\ hrs.]{4NH_2OH} C_4H_3O{-}CH(NHOH){-}CH_2COOH +$$

III

$$C_4H_3O{-}CH(NH_2){-}CH_2{-}COOH + C_4H_3O{-}C(=N{-}O{-}C(=O){-}CH_2) + C_4H_3O{-}C(=NOH){-}CH_3$$

IV V VI

2-(2-Nitrovinyl)furan, VII, is obtained as one product of the action of

nitrogen dioxide on furylacrylic acid. Presumably this reaction involves formation of the intermediate addition product shown below.[156]

$$C_4H_3O{-}CH{=}CHCOOH \xrightarrow{2NO_2}$$

$$C_4H_3O{-}CH(ONO){-}CHNO_2COOH \xrightarrow[-CO_2]{-HONO} C_4H_3O{-}CH{=}CHNO_2$$

VII

There is no reported attempt to add hydrogen cyanide to furylacrylic acid. However, Sandelin[21, 111] added this reagent to furfurylidenemalonic ester in basic solution, reaction proceeding with hydrolysis and loss of carbon dioxide and formation of 3-(2-furyl)-3-cyanopropionic acid, VIII, in 25 per cent yield.

$$C_4H_3O{-}CH{=}C(COOR)_2 \xrightarrow{HCN} C_4H_3O{-}CH(CN){-}CH_2COOH$$

VIII

The addition of sodium or potassium bisulfite to furylacrylic acid and to α-cyanofurylacrylic acid and their derivatives produces the expected sulfonic acid salts as indicated.[198, 199]

$$\left.\begin{matrix} C_4H_3O{-}CH{=}CH{-}COOH \\ \quad\quad\quad\quad -COOR \\ \quad\quad\quad\quad -CONH_2 \\ \quad\quad\quad\quad -CN \end{matrix}\right\} \xrightarrow{NaHSO_3} \left\{\begin{matrix} SO_3Na \\ | \\ C_4H_3O{-}CH{-}CH_2{-}COOH \\ \quad\quad\quad\quad\quad\quad -COOR \\ \quad\quad\quad\quad\quad\quad -CONH_2 \\ \quad\quad\quad\quad\quad\quad -CN \end{matrix}\right.$$

While it has not been attempted to add a simple mercaptan to an α,β-unsaturated furylalkenoic acid, ethanedithiol is reported to react with two moles of furylacrylic ester in the presence of piperidine to give 3,8-difuryl-4,7-dithiadecanedioic ester, IX.[200]

$$2C_4H_3O{-}CH{=}CHCOOR + HS{-}CH_2CH_2{-}SH \rightarrow$$

$$\begin{matrix} C_4H_3O{-}CH{-}CH_2{-}COOR \\ | \\ S \\ | \\ (CH_2)_2 \\ | \\ S \\ | \\ C_4H_3O{-}CH{-}CH_2COOR \end{matrix}$$

IX

[198] Thurston (to American Cyanamid Co.) U. S. Pat. 2,385,314 (1945); *C. A.*, **40**, 609 (1946).

[199] Thurston (to American Cyanamid Co.) U. S. Pats. 2,402,511–513 (1946); *C. A.*, **41**, 158 (1947).

[200] Langkammerer (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,393,327 (1946); *C. A.*, **40**, 3467 (1946).

Treatment of furylacrylic acid with ethanolic hydrogen chloride produces a very interesting result, first discovered by Marckwald[18] (see also [130]). From the reaction mixture, he isolated 3-pentanone-1,5-dicarboxylic ester (4-ketopimelic ester), X (R = H), in approximately 60 per cent yield. In a similar manner, 3-heptanone-1,5-dicarboxylic ester (X, R = C_2H_5) may be obtained in almost quantitative yield from 3-(2-furyl)-2-ethylacrylic acid.[27] The reaction, which has since been applied with varying success to a number of compounds possessing the general grouping C_4H_3O—CH=CR—CO–, involves hydrolytic fission of the furan nucleus and an intramolecular oxidation-reduction. A mechanism to explain the reaction is proposed elsewhere (see p. 652).

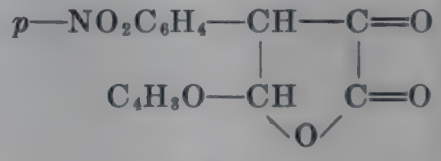
$$C_4H_3O\text{—}CH{=}CRCOOH \xrightarrow[EtOH]{HCl} HOOCCH_2CH_2COCH_2CHRCOOH$$

X

Furylalkenoic Acids with Functional Substituents in the Side Chain

Keto Acids. The acids of this classification were obtained, for the most part, by condensation of furfural with aliphatic keto acids or esters. In this way, pyruvic acid is converted into furfurylidenepyruvic acid. On the other hand, when furfural is condensed with *p*-nitrophenylpyruvic ester under the influence of potassium ethoxide, the reaction follows a different course with formation of the butyrolactone derivative, I (m.p. 201°, dec.). With alkali, I decomposes with regeneration of furfural and the ketonic acid.[201]

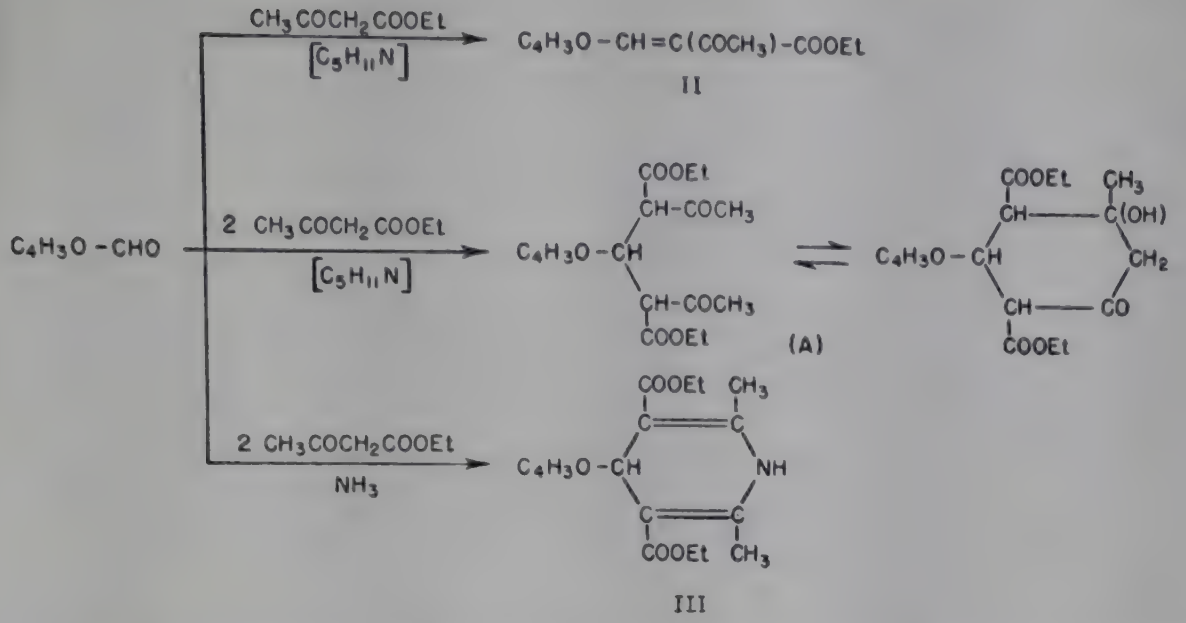
$$C_4H_3O\text{—}CHO + p\text{—}NO_2C_6H_4CH_2COCOOEt \xrightarrow[[EtOK]]{-EtOH}$$



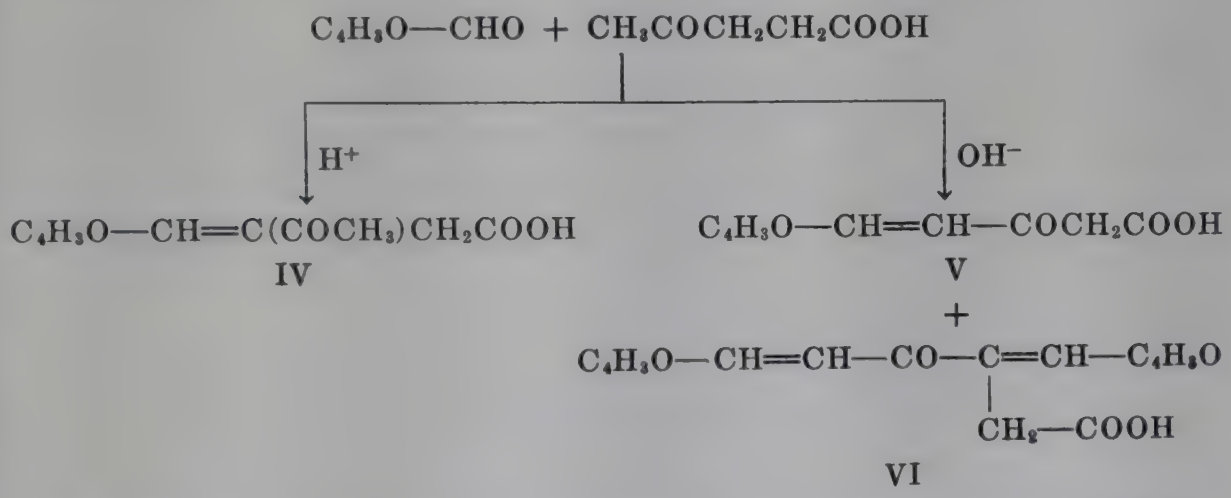
I

With acetoacetic ester, furfural may give rise to a variety of products, depending upon the ratio of reactants, the condensing agent employed, and other factors. Equimolecular proportions in glacial acetic acid, or in the presence of a small amount of piperidine give mainly the expected α-furfurylideneacetoacetic ester, II. With two moles of the ester and piperidine as a catalyst, furfural is converted into furfurylidenebisacetoacetic ester, A (p. 612). By carrying out the latter reaction in alcoholic ammonia, condensation results in the formation of 4-(2-furyl)-1,4-dihydro-3,5-lutidinedicarboxylic ester, III, m.p. 164°.[202, 203]

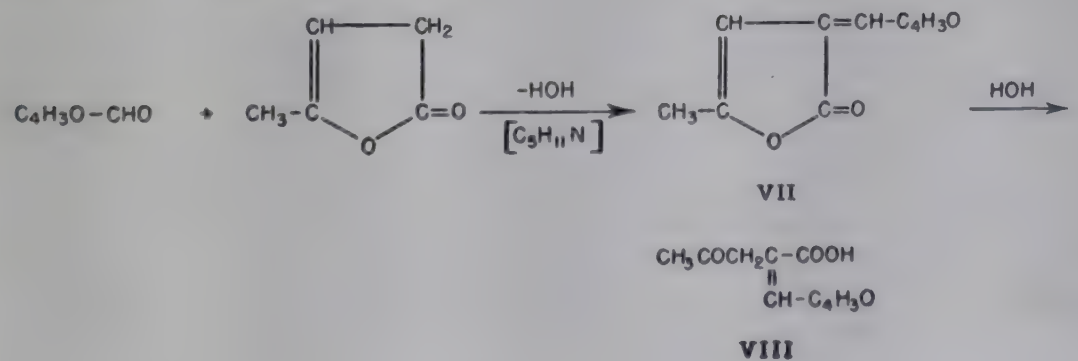
[201] Cordier and Cagniant, *Compt. rend.*, **228**, 1130 (1949).
[202] Schiff and Puliti, *Ber.*, **16**, 1607 (1883).
[203] Heiber, *Ber.*, **25**, 2405 (1892).



In the condensation of furfural with levulinic acid, acidic conditions promote reaction at the β-carbon atom (IV), whereas in alkaline medium, δ-furfurylidenelevulinic acid, V, is the major product, along with some of the β,δ-difurfurylidene condensation product, VI. α-Furfurylidenelevulinic



acid, VIII, is also known, the preparation involving hydrolysis of 2-furfurylidene-4-methyl-3-butenoic γ-lactone (VII, m.p. 78–79°) derived from furfural and α-angelica lactone.



Furfurylidenepyruvic acid (furylacrylylformic acid): $C_4H_3O—CH=CH—CO—COOH$; m.p. 110–111, 112°; **phenylhydrazone,** m.p. 164–165°; **ethyl ester,** m.p. 44–45°. Formed by condensation of furfural with pyruvic acid in hot glacial acetic acid,[122] or in cold aqueous alkali.[6, 204] Oxidation with hydrogen peroxide gives rise to furylacrylic acid in quantitative yield.[204] Reduction with sodium amalgam yields a mixture of products containing some 4-(2-furyl)-2-hydroxycrotonic acid, although this compound could not be obtained in crystalline form.[205]

Furylacrylylacetic acid: $C_4H_3O—CH=CH—COCH_2COOH$. **Ethyl ester,** m.p. 60°, obtained by careful hydrolytic cleavage of furylacrylylacetoacetic ester (below).[206]

α-Furfurylideneacetoacetic acid: II (text). **Ethyl ester,** b.p. 188–189° (30 mm.), obtained by condensation of equimolecular proportions of furfural and acetoacetic ester in glacial acetic acid,[207] or under the influence of a small amount of piperidine[208] (see also [102]). The ester adds organomagnesium halides, under appropriate conditions, to give on subsequent hydrolysis the corresponding 3-(2-furyl)-2-acetylalkenoic acids.[45] By the action of alcoholic ammonia, the ester is converted into ethyl 4-(2-furyl)-1,4-dihydro-3,5-lutidinedicarboxylate.[209]

α-Furfurylidenefuroylacetic acid*: $C_4H_3O—CH=C(CO—C_4H_3O)—COOH$. **Ethyl ester,** b.p. 206–214° (6 mm.), from furfural and ethyl furoylacetate heated at reflux in acetic anhydride for 24 hours.[102]

α-Furfurylidenebenzoylacetic acid: $C_4H_3O—CH=C(COC_6H_5)—COOH$. **Ethyl ester,** m.p. 68°, from furfural and ethyl benzoylacetate in acetic anhydride at 150° for 3 hours[210] (see also [102]).

α-Furfurylidenelevulinic acid: VIII (text); m.p. 125–126°; by hydrolysis of the condensation product of furfural and α-angelica lactone.[66]

β-Furfurylidenelevulinic acid: IV (text); m.p. 153°; **phenylhydrazone,** m.p. 168°. On slow distillation, the acid loses the elements of water to form a compound, $C_{10}H_8O_3$ (m.p. 190°) which is reported to be 4-hydroxy-6-acetocoumarone[109] (see also [210a, 37]). Reduction of the acid with Na-Hg gives rise to β-furfuryllevulinic acid.[66, 109]

δ-Furfurylidenelevulinic acid: V (text); m.p. 115–116°. Treatment with alcoholic hydrogen chloride produces 3,6-octanedione-1,8-dicarboxylic acid [dilevulinic acid; $(CH_2COCH_2CH_2COOH)_2$] in low yield.[211, 212]

β,δ-Difurfurylidenelevulinic acid: VI (text); m.p. 148°.[109]

β-(5-Isopropylfurfurylidene)levulinic acid:

$$i\text{-}C_3H_7—C_4H_2O—CH=C(COCH_3)CH_2COOH$$

m.p. 136°.[213]

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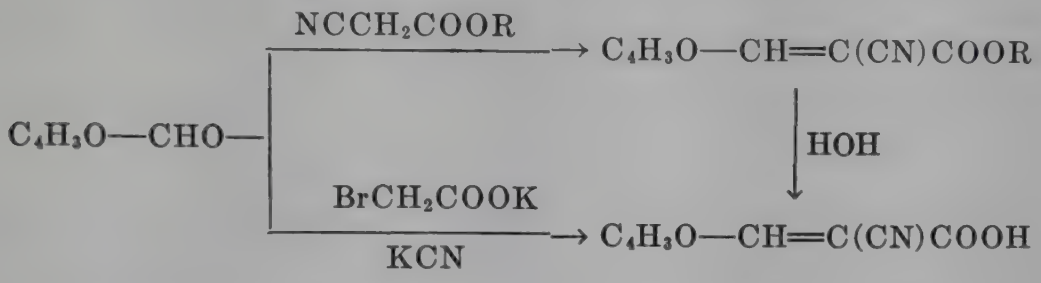
* Dohrn and Hamann[102] refer to this compound as "α-furfurylidene-furylacetic acid" derived from furfural and "furylacetic ester" rather than "furoylacetic ester" as indicated above. This must have been a typographical error, since following reduction, the product formed a substituted pyrazolone with phenylhydrazine, showing that it is a β-keto ester.

[204] Friedmann, *Helv. Chim. Acta*, **14**, 783 (1931).
[205] Bougault, *Ann. chim.* (*8*), **14**, 145 (1908).
[206] English and Lapides, *J. Am. Chem. Soc.*, **65**, 2466 (1943).
[207] Claisen and Matthews, *Ann.*, **218**, 176 (1883).
[208] Knoevenagel, *Ber.*, **31**, 730 (1898).
[209] Ruhemann, *J. Chem. Soc.*, **83**, 374 (1903).
[210] Perkin and Stenhouse, *J. Chem. Soc.*, **59**, 996 (1891).
[210a] Sen and Roy, *J. Indian Chem. Soc.*, **7**, 401 (1930).
[211] Hofacker and Kehrer, *Ber.*, **28**, 917 (1895).
[212] Kehrer and Hofacker, *Ann.*, **294**, 165 (1897).

Furylacrylylacetoacetic acid: $C_4H_3O—CH=CH—CO—CH(COCH_3)—COOH$. **Ethyl ester,** m.p. 50–52°, by the action of furylacrylyl chloride on sodioacetoacetic ester in ether[214] (see also [206]).

Furylacrylyltetronic acid: $C_4H_3O—CH=CH—CO—C=C(OH)—CH_2$; m.p. 146–148°, by condensation of furfural with α-acetyltetronic acid.[215]

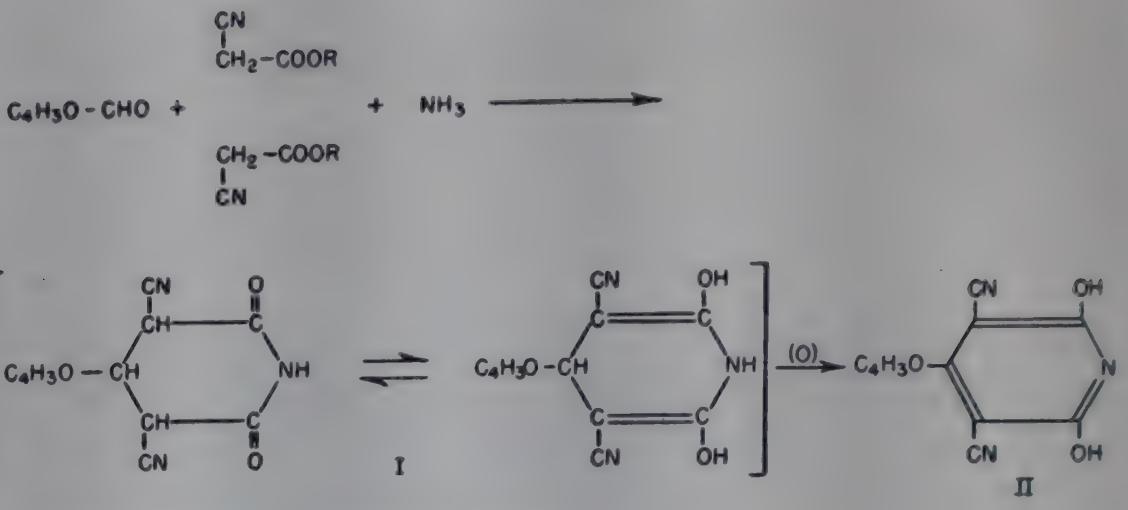
Cyano Acids. Condensation of furfural with cyanoacetic ester, in the presence of an amine or sodium ethoxide, proceeds in normal fashion giving rise to 3-(2-furyl)-2-cyanoacrylic ester.[181, 216, 217, 218] Beccari[219] reports that hydrofuramide may be substituted for furfural, and Clarke and Francis[220] obtained the cyano acid in quantitative yield by condensation of furfural with potassium bromoacetate and potassium cyanide in the cold.



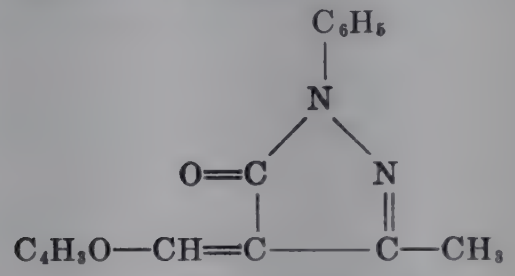
3-(2-Furyl)-2-cyanoacrylic acid (furfurylidenecyanoacetic acid); m.p. 218°; **ethyl ester,** m.p. 94°, b.p. 295–300°; **acid chloride,** m.p. 79°. The **amide,** m.p. 156°, prepared from the chloride and ammonia or directly from furfural and cyanacetamide, is converted into furfurylidenemalonitrile, m.p. 76°, by the action of phosphorus pentachloride.[181, 221]

When two molecular proportions of cyanoacetic ester were condensed with furfural in aqueous ammonia, Guareschi[217] obtained as the sole product, a crystalline material (m.p. 260–265°) which he formulated as 4-furyl-2,6-dihydroxy-3,5-dicyanopyridine, II. Since the expected product is the dihydropyridine derivative, I (shown in the keto and enol forms), Guareschi's report implies facile oxidation of I to II during the course of reaction or in the step of isolation.

[213] Reichstein and Hirt, *Helv. Chim. Acta*, **16**, 121 (1933).
[214] Lampe, Rosenblumowna and Kessel, *Chem. Listy*, **26**, 454 (1932); *C. A.*, **27**, 721 (1933).
[215] Baker, Grice and Jansen, *J. Chem. Soc.*, **1943**, 241.
[216] Bechert, *J. prakt. Chem.*, **50**, 16 (1894).
[217] Guareschi, *Atti accad. sci. Torino*, **34**, 30 (1899); *Chem. Centr.*, **1899, II**, 118.
[218] Bertini, *Gazz. chim. ital.*, **31, I**, 265 (1901).
[219] Beccari, *Atti accad. sci. Torino*, **37**, 29 (1901); *Chem. Centr.*, **1902, II**, 740.
[220] Clarke and Francis, *Ber.*, **44**, 273 (1911).
[221] Heuck, *Ber.*, **28**, 2251 (1895).

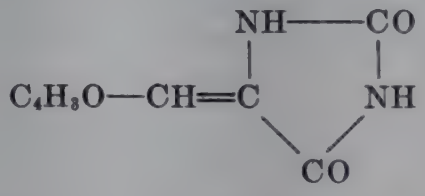


4-Furfurylidene-1-phenyl-3-methyl-5-pyrazolone:



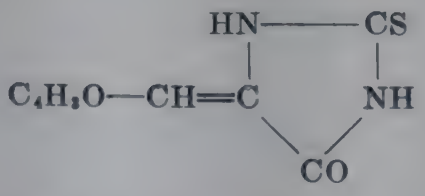
violet needles, m.p. 111–112°, by condensation of furfural with the appropriate substituted pyrazolone. On heating an alcoholic solution of the compound with an additional quantity of the latter there is produced furfurylidenebisphenylmethylpyrazolone, m.p. 172–173°.[222]

Furfurylidenehydantoin:



m.p. 232, 239–240°; from furfural and hydantoin on heating with fused sodium acetate.[223] Dissolves in concentrated H_2SO_4 with intense green coloration.[224] Reduction with sodium amalgam produced furfurylhydantoin which gives rise to furylalanine on hydrolysis with barium hydroxide.[77]

Furfurylidenethiohydantoin:



m.p. 255° (dec.); from furfural and benzoyl- or acetyl-thiohydantoin in glacial acetic acid with sodium acetate.[225]

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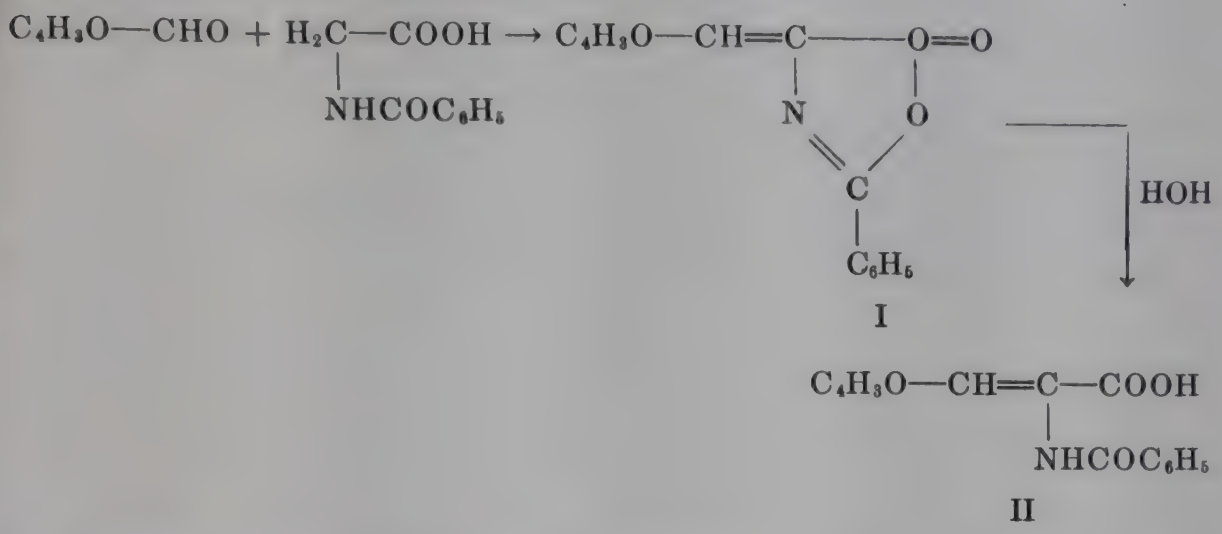
[222] Tambor, *Ber.*, **33**, 864 (1900).

[223] du Vigneaud, McKennis, Simmonds, Dittmer and Brown, *J. Biol. Chem.*, **159**, 385 (1945).

[224] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 568 (1911).

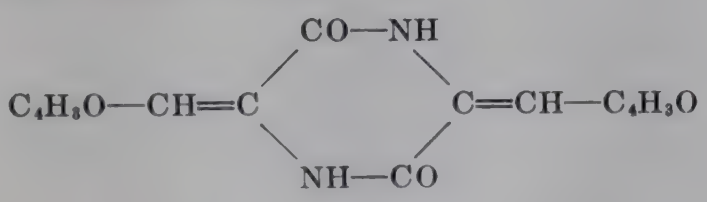
[225] Wheeler and Hoffman, *Am. Chem. J.*, **45**, 371 (1911).

Amino Acids and Derivatives. Hippuric acid condenses with furfural on heating in the presence of sodium acetate and acetic anhydride[226, 76, 81] to form 3-(2-furyl)-2-benzamidoacrylic acid (furfurylidenehippuric acid), II, in the form of its azlactone, 2-phenyl-4-furfurylidene-5-oxazole, I. When heated with dilute alkali, I is converted into II.



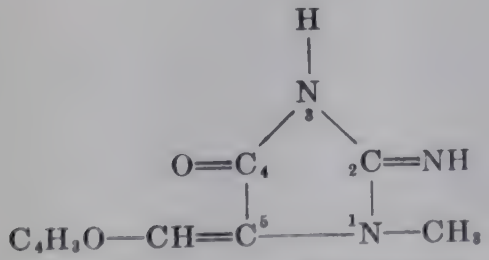
Furfurylidenehippuric acid: m.p. 210°; **methyl ester,** m.p. 141°; **ethyl ester,** m.p. 132–133°. The azlactone melts at 171°, and is converted by piperidine in alcohol to the **piperidide** of the free acid, m.p. 162–163°. Similarly, the action of ammonia in alcohol produces the **amide,** m.p. 184°, which on warming with alkali cyclizes with loss of water to give the imidazolone derivative (I above, where the hetero oxygen atom is replaced by —NH—), m.p. 241° (dec.).[226] For the reaction of II with hydroxylamine, see [81]. For reduction of II to obtain furylalanine, see Flatow.[76]

3,6-Difurfurylidene-2,5-diketopiperazine:



m.p. 289–290° (dec.) in 84 per cent yield by condensation of furfural with 2,5-diketopiperazine in acetic anhydride in the presence of sodium acetate. Reduction and subsequent hydrolysis produces furylalanine.[75] The related product derived from 5-(acetoxymethyl)furfural and the diketopiperazine melts at 220° (dec.)[196]

Furfurylidenecreatinine:



[226] Erlenmeyer and Stadlin, *Ann.*, **337**, 283 (1904).

III; silvery needles, m.p. 273° dec.); by condensing furfural with creatinine. **Picrate,** m.p. 244° (dec.); **hydrochloride,** m.p. 257° (dec.)[227] (see also [228]). Treatment of III with warm, aqueous sodium hydroxide results in the formation of furfurylidenecreatine, C_4H_3O—CH=C(COOH)—N(CH_3)—C(NH)NH_2, m.p. 254° (dec.). **Acetyl derivative** of III, m.p. 252°, is reduced to the corresponding furfurylacetylcreatinine, m.p. 189°. Alkylation of III with methyl sulfate produces N^2-methyl-5-furfurylidenecreatinine, m.p. 132°, which is also obtained directly from furfural and methylcreatinine sulfate.[229]

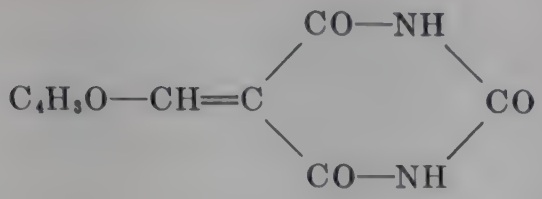
Furylalkenedioic Acids and Related Polycarboxylic Acids

The simplest member of this class is furfurylidenemalonic acid, produced as the ethyl ester by reaction of furfural with malonic ester using ammonia,[147] or piperidine[230, 231] as condensing agents. Earlier, Marckwald[20] (see also [146, 21, 112]) prepared the ester by heating the reactants in acetic anhydride, a procedure which, in the hands of Hinz, Meyer and Schücking,[6] resulted in an 80 per cent yield of product. For additional reference to the preparation of furfurylidenemalonic acid and its derivatives, the work of Claisen and Matthews,[207] Liebermann,[146] Heuck,[221] Dakin,[232] Boehm,[233] Dalal and Dutt[234] and Kiprianov and Kusner[235] may be consulted. The monoethyl and dipentyl esters are reported to be useful insecticides.[236]

Furfurylidenemalonic acid: C_4H_3O—CH=C$(COOH)_2$; m.p. 203, 205, 207.5°. **Diethyl ester,** m.p. 42–43°, b.p. 172–175° (9 mm.); **dipentyl ester,** b.p. 147° (0.5 mm.); **diamide,** m.p. 200°; **dinitrile,** m.p. 76°. For the ethanolamine salt, m.p. 137° (dec.), obtained directly from furfural, malonic acid and ethanolamine, see Kiprianov and Kusner.[235] For reaction of the ester with the Grignard reagent, see Maxim and Georgescu[45]; with KCN, see Sandelin.[21, 112] Aniline adds across the lateral double bond of the ester to give ethyl 2-(2-furyl)-2-anilino-1,1-ethanedicarboxylate, m.p. 72–73°.[237] Catalytic hydrogenation of the ester over Raney nickel at 100–130° yields tetrahydrofurfurylmalonic ester, b.p. 150–151° (10 mm.) in 96 per cent yield; at 160–175° there is obtained 3-tetrahydrofurylpropionic ester and a product of unknown constitution.[6]
Furfurylidenebarbituric acid: (furfurylidenemalonylurea);

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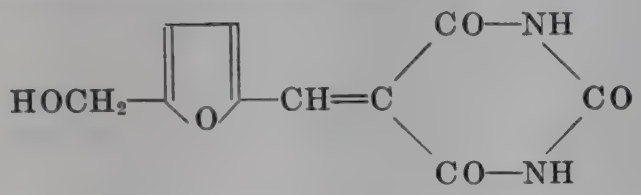
[227] Cornthwaite and Jordan, *J. Am. Chem. Soc.*, **56,** 2733 (1934).
[228] Cattaneo, Deulofeu and Guerrero, *Ber.*, **72,** 1461 (1939).
[229] Cornthwaite, *J. Am. Chem. Soc.*, **59,** 1616 (1937).
[230] Knoevenagel, *Ber.*, **31,** 2585 (1898).
[231] Knoevenagel, *Ann.*, **402,** 111 (1914).
[232] Dakin, *J. Biol. Chem.*, **7,** 49 (1909).
[233] Boehm, *Arch. Pharm.*, **267,** 129 (1929); *Chem. Centr.*, **1929, I,** 2183.
[234] Dalal and Dutt, *J. Indian Chem. Soc.*, **9,** 309 (1932); *C. A.*, **27,** 279 (1933).
[235] Kiprianov and Kusner, *J. Gen. Chem. U.S.S.R.*, **6,** 641 (1936); *C. A.*, **30,** 6350 (1936).
[236] Roblin and Hechenbleikner (to American Cyanamid Co.), U. S. Pat. 2,293,309 (1943); *C. A.*, **37,** 1007 (1943).
[237] Goldstein, *Ber.*, **28,** 1450 (1895).



from furfural and barbituric acid in hot, aqueous solution. The compound decomposes above 280°.[238, 239]

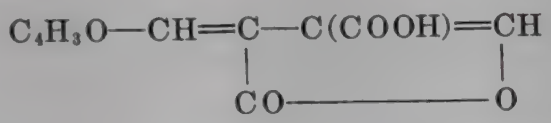
5-(Hydroxymethyl)furfurylidenemalonic acid: $HOCH_2—C_4H_2O—CH=C(COOH)_2$; obtained by heating equimolecular proportions of 5-(hydroxymethyl)furfural and malonic acid together with a small amount of diethylamine. The product was recrystallized from diethyl oxalate in the form of a fine powder, the color of sand. On heating to 130°, carbon dioxide was evolved, presumably with formation of (hydroxymethyl)furylacrylic acid. **Diethyl ester:** m.p. 48.5°, b.p. 221° (11 mm.), d_4^{59} 1.1648, n_D^{59} 1.539, $n_{H\alpha}^{59}$ 1.536; prepared as above using malonic ester in place of the free acid.[240]

5-(Hydroxymethyl)furfurylidenebarbituric acid:



m.p. 274°; in 99 per cent yield from 5-(hydroxymethyl)furfural and barbituric acid. When fed orally to dogs and rabbits, it is eliminated in the urine as 5-hydroxymethyl-2-furoic acid (15–20 per cent of the theoretical).[241]

Furfurylideneaconic acid:



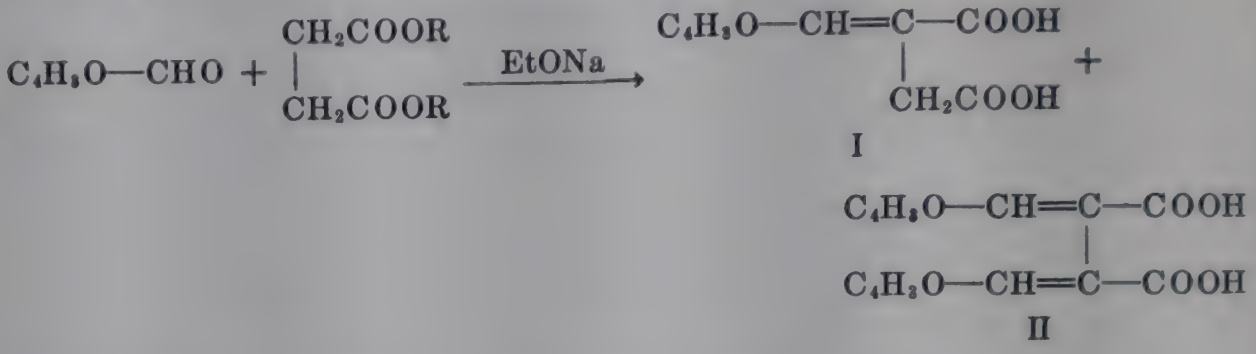
darkens at 290°, but does not melt. Obtained by condensation of furfural with aconic acid in the presence of a few drops of ethylamine.[242]

4-(2-Furyl)-1,3-butadiene-1,1-dicarboxylic acid: $C_4H_3O—CH=CHCH=C(COOH)_2$; m.p. 186, 190–195° (dec.) by condensation of furylacrolein with malonic acid in pyridine containing a trace of piperidine.[33, 52] The **diethyl ester,** b.p. 210–211° (33 mm.) is obtained by heating malonic ester with the aldehyde in acetic anhydride.[122]

Condensation of furfural with succinic ester leads to the formation of 2-furfurylidenesuccinic acid, I, and 2,3-difurfurylidenesuccinic acid, II, the relative amounts depending upon the ratio of reactants employed. Using equimolecular proportions, a considerable amount of I is found in

[238] Conrad and Reinbach, *Ber.*, **34,** 1339 (1901).
[239] Ridi and Papini, *Gazz. chim. ital.*, **76,** 369 (1946); *C. A.*, **42,** 1283 (1948).
[240] Middendorp, *Rec. trav. chim.*, **38,** 1 (1919).
[241] Iseki, *J. Biochem. Japan*, **19,** 7 (1934); *C. A.*, **28,** 2709 (1934).
[242] Shemyakin and Red'kin, *J. Gen. Chem. U.S.S.R.*, **9,** 442 (1939); *C. A.*, **34,** 88 (1940).

the reaction mixture, and as expected, an excess of furfural increases the yield of the bimolecular condensation product[243] (see also [114, 244]).



I

II

2-Furfurylidenesuccinic acid: I; decomposes between 205–215°.[114]

3-Furfurylidene-2,2-dimethylsuccinic acid:

$$C_4H_3O—CH=C(COOH)—C(CH_3)_2—COOH$$

m.p. 218° (dec.) from furfural and dimethylitaconic ester in the presence of sodium ethoxide. **Anhydride,** m.p. 63°.[243]

3-Furfurylidene-2,2-diphenylsuccinic acid:

$$C_4H_3O—CH=C(COOH)—C(C_6H_5)_2—COOH$$

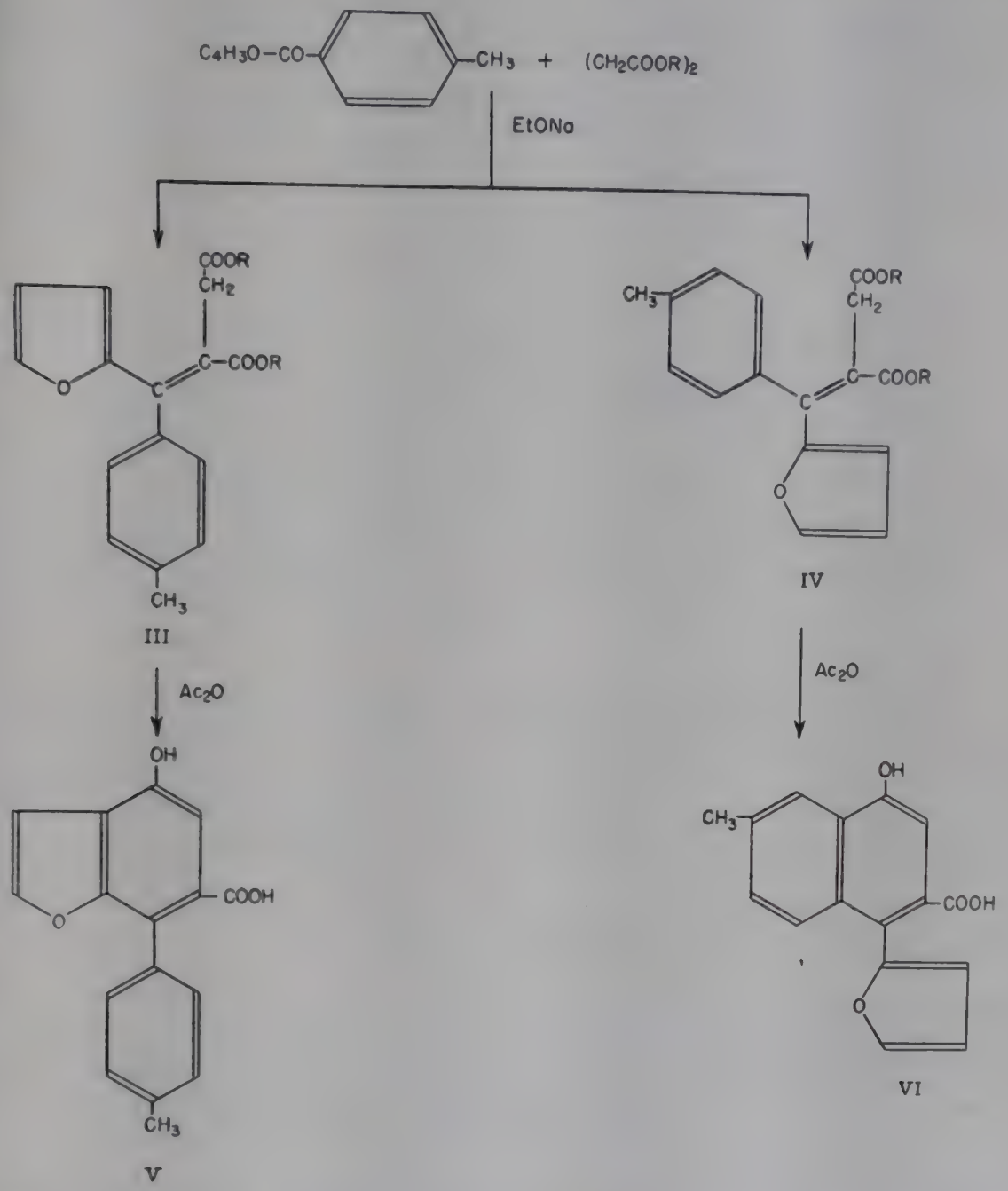
m.p. 202° (dec.) prepared as in preceding case using diphenylitaconic ester. **Anhydride,** m.p. 156°.[243]

2,3-Difurfurylidenesuccinic acid: II. The melting point of this acid has been variously reported as 185–187°,[244] 217–225°[114] and 227–228°.[243] **Anhydride,** m.p. 187°,[244] 204°.[243]

The related condensation of aryl furyl ketones with succinic ester was carried out by Borsche and Leditschke[245] to obtain disubstituted itaconic esters. These investigators were primarily interested in the products obtained from the latter on dehydration, it being anticipated that loss of water would occur intramolecularly with cyclization to condensed ring systems. From *p*-tolyl furyl ketone and succinic ester they obtained a resinous, non-crystallizable material in which, apparently, both of the stereoisomeric forms of 2-(ω-*p*-tolylfurfurylidene)succinic ester (III and IV) were present. On heating the crude mixture with acetic anhydride and sodium acetate, two compounds were isolated which were assigned the coumarone, V, and naphthalene, VI, structures shown below. Comparison of the isolated yields of V and VI suggests that III is the predominant product in the first step of reaction. In this regard, Borsche and Leditschke were able to obtain (in crystalline form from the initial crude product) the appropriately modified itaconic esters of configuration III following condensation of succinic ester with *p*-methoxyphenyl furyl ketone and

[243] Stobbe and Eckert, *Ber.*, **38**, 4075 (1905).
[244] Titherley and Spencer, *J. Chem. Soc.*, **85**, 183 (1904).
[245] Borsche and Leditschke, *Ann.*, **529**, 108 (1937).

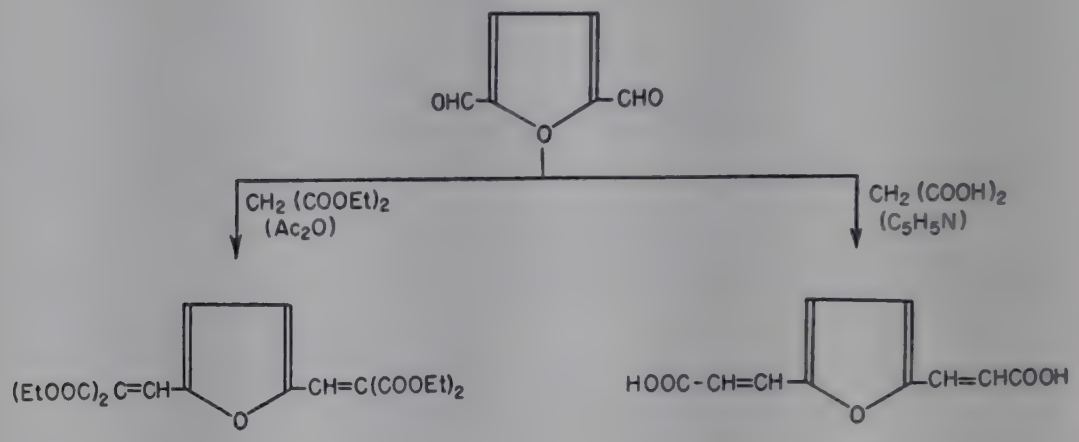
with 3,4-dimethoxyphenyl furyl ketone (see also the more recent work of Knott [246]).



The condensation of 2,5-furandicarbonal with malonic acid and ester was studied by Cooper and Nuttall.[36] With malonic ester in acetic anhydride there is formed the expected tetracarboxylic ester, ethyl 2,5-furanbis(methylenemalonate), VII, which on saponification is converted into the free acid. The latter, on recrystallization from glacial acetic acid, forms a brown solid material; analysis indicates an unstable equimolecular addition compound of the tetracarboxylic acid and acetic acid. An isomeric form of this complex, red in color, is obtainable by condensing 2,5-furan-

[246] Knott, *J. Chem. Soc.*, **1945**, 189.

dicarbonal with malonic acid using acetic acid as the catalyst. Neither of these addition products melts, but on heating they evolve acetic acid and on esterification with ethyl alcohol and hydrogen chloride they change into VII. If, instead of acetic acid, pyridine is used as the condensing agent, reaction of the dialdehyde with malonic acid proceeds with evolution of carbon dioxide and the formation of a mixture of the isomeric forms of 2,5-furandiacrylic acid, VIII.



VII VIII

2,5-Furandiacrylic acid, VIII; no constants reported. **Dimethyl ester,** m.p. 152–153°; **diethyl ester,** m.p. 110–111°. Reduction of the acid with sodium amalgam produced furan-2,5-dipropionic acid, whereas with aluminum powder in alkali there was obtained an intermediate reduction product, m.p. 183–184° containing only two more hydrogen atoms than the original acid. The constitution of this intermediate is unknown[36] (see also [247]).

2,5-Furanbis(methylenemalonic acid), VII; no constants reported. Obtained by saponification of the **diethyl ester,** m.p. 90–91°.[36]

Miscellaneous Dienoic Acids

Furfurylidenecrotonic acid [4-(2-furyl)-1,3-butadiene-1-carboxylic acid]:

$$C_4H_3O{-}(CH{=}CH)_2{-}COOH$$

m.p. 153–154, 158–159°; obtained by Perkin reaction from 3-(2-furyl)acrolein, acetic anhydride and sodium acetate[122]; also by decarboxylation of 4-(2-furyl)-1,3-butadiene-1,1-dicarboxylic acid derived from furylacrolein and malonic acid[33] (see also [52, 248]). The **ethyl ester,** m.p. 14–15°, b.p. 145–150° (10 mm.) was obtained in 73 per cent yield by Claisen condensation of furylacrolein and ethyl acetate in the presence of sodium.[6] Hydrogenation of the ester over Raney nickel gave a 90 per cent yield of ethyl 5-tetrahydrofurylvalerate.[6]

4-Furfurylidene-3-methylcrotonic acid [4-(2-furyl)-2-methyl-1,3-butadiene-1-carboxylic acid]; $C_4H_3O{-}CH{=}CH{-}C(CH_3){=}CH{-}COOH$; m.p. 127°, by condensa-

[247] Asahina and Fujita, *J. Pharm. Soc. Japan*, **461**, 583 (1920); *C. A.*, **14**, 3227 (1920).

[248] Cupery (to E. I. du Pont de Nemours & Co.) U. S. Pat. 2,381,880 (1945); *C. A.*, **39**, 5093 (1945).

tion of furfural with 3-methylcrotonic anhydride under the influence of triethylamine.[249]

4-Furfurylidene-4-chlorocrotonic acid [4-(2-furyl)-3-chloro-1,3-butadiene-1-carboxylic acid]; $C_4H_3O—CH=CCl—CH=CH—COOH$; m.p. *ca.* 168° by the Perkin reaction with 3-(2-furyl)-2-chloroacrolein and sodium acetate in acetic anhydride.[192]

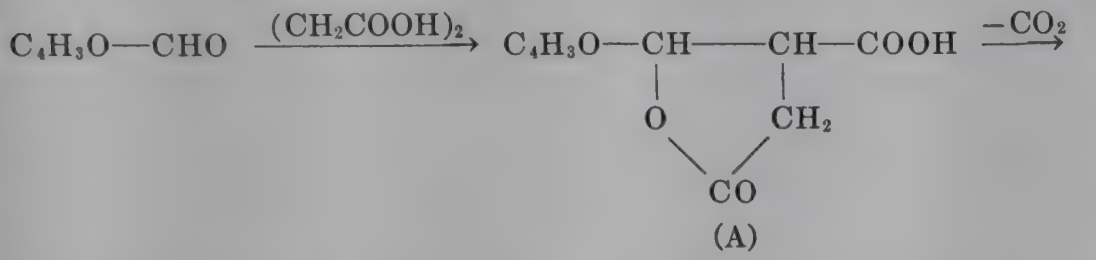
4-Furfurylidene-2-phenylcrotonic acid [4-(2-furyl)-1-phenyl-1,3-butadiene-1-carboxylic acid]: $C_4H_3O—CH=CH=C(C_6H_5)—COOH$; m.p. 212–213°; by condensation of furylacrolein with sodium phenylacetate in acetic anhydride.[122]

1-(2-Furyl)-1,3-pentadiene-1-carboxylic acid (crotylidenefurylacetic acid):

$$C_4H_3O—C(COOH)=CH—CH=CH—CH_3$$

by the Reformatsky reaction from furylbromoacetic ester and crotonaldehyde. No constants given. Esters are reported to be excellent drying oil substitutes.[248]

1,4-Di(2-furyl)-1,3-butadiene-2-carboxylic acid (2,3-difurfurylidenepropionic acid): I; m.p. 195–197° (dec.); by condensation of equimolecular proportions of furfural and sodium succinate in acetic anhydride.[114] While none of the intermediate products could be found, it was postulated that this reaction proceeded by way of γ-furylparaconic acid (A) followed by loss of carbon dioxide to give furylisocrotonic acid (B), and finally condensation of the latter with another molecule of furfural. On



(A)



I

reduction with sodium amalgam, I adds two atoms of hydrogen to form a crystalline product, m.p. 66–67°, designated as 3-furfurylidene-2-furfurylpropionic acid, $C_4H_3O—CH=CH—CH(CH_2—C_4H_3O)—COOH$.[114]

Furfurylidenecrotonylformic acid: $C_4H_3O—(CH=CH)_2—CO—COOH$; from furylacrolein and pyruvic acid in acetic acid. No constants reported.[122]

3-(2-Furyl)propiolic Acid

The only reported furylalkynoic acid is 3-(2-furyl)propiolic acid, $C_4H_3O—C\equiv C—COOH$ (m.p. 113–114°, dec.). It was prepared from 2-furylacetylene by treatment with ethylmagnesium bromide and subsequent carbonation,[140] and by reduction of the 5-bromo substitution product using zinc dust in aqueous ammonia.[250] The acid is very soluble in alcohol, ether, chloroform and ethyl acetate. It is less soluble in benzene, and only slightly soluble in ligroin.

[249] Ishikawa and Kojima, *Science Repts. Tokyo Bunrika Daigaku*, **1**, 289 (1934); *C. A.*, **28**, 2697 (1934).

[250] Gilman, Hewlett and Wright, *J. Am. Chem. Soc.*, **53**, 4192 (1931).

Chapter 14

HYDROLYTIC AND AMMONOLYTIC CLEAVAGE OF THE FURAN NUCLEUS

One of the most interesting facets of the behavior of furan types is the chemistry of those reactions involving rupture of the nucleus. This has been accomplished under a wide variety of conditions, but in general, the subject can be divided into two broad categories, oxidizing[a] and non-oxidizing cleavage. In large measure, the products of these reactions are 1,4-difunctional olefinic and aliphatic compounds. It is also considered to be within the scope of this chapter, however, to include those nuclear transformation reactions whereby furans are converted into other heterocyclic types (pyridines, pyrroles, thiophenes), since these must be thought to involve ring rupture at some intermediate stage. On the other hand, cleavage by hydrogenolysis is more appropriately dealt with elsewhere (see p. 676), and for this reason is omitted from the present discussion.

From a purely theoretical standpoint, elucidation of the course of ring cleavage under various conditions would be a satisfying achievement. Beyond this, however, there are a number of practical considerations which offer inducement to the investigator to pursue this phase of furan chemistry. For example, ring opening is frequently encountered as a bothersome side-reaction in many syntheses with furan types. In these instances it would be most helpful if cleavage could be minimized yet further, or possibly eliminated entirely. Conversely, a complete understanding of the mechanism might permit the selection of experimental conditions whereby cleavage could be made the major, or sole course of reaction, and thus open the way for the production of new compounds of possible commercial value. Considerable progress has been made along these lines during the past several years, but a great deal of work remains to be done. There are many gaps in our present knowledge and it is hoped that the following discussion will serve as a stimulant to further research in this potentially fruitful field.

Furan compounds in general are subject to cleavage by acidic (electron acceptor) reagents in aqueous or alcoholic medium. Stability under these conditions varies widely depending upon the nature and number of substituent groups. Similarly, the furans exhibit widely divergent stabilities in

[a] Throughout the book there are many references to oxidation reactions leading to open-chain products. Particularly, the reader is referred to the detailed discussions given in chapters 9, 12.

basic systems. Certain types (nitrofurans, furoin, etc.) are very sensitive toward basic (electron donor) reagents, and as will be shown, the ring in acylfurans may be ruptured by aqueous alkali, and by nitrogen bases. In many instances the course of these reactions is obscured by the formation of resinous tars of unknown constitution, but enough simple products have been isolated to permit formulation, in a preliminary manner, of a concept which fits all of them into one general pattern. Briefly stated, the key step leading to non-oxidizing cleavage of furan compounds in ionic medium (acidic or basic) appears to involve coordination of a suitable donor *reagent* or *group* with an alpha carbon atom of the nucleus.

The ease with which this coordination can occur is, of course, a function of electron availability in the furan ring which, in turn, varies with the type of substituent group(s). Thus, substituents which exert a strong electron-withdrawal effect decrease the electron density and create a relatively electropositive center in the nucleus. As a consequence, furan compounds of this category are found to be subject to direct nuclear attack by basic reagents or groups (NH_3, OH^-, etc.), although this is not necessarily the major course of reaction. That is, the attack may be largely confined to the substituent group as, for example, in the formation of aldimines from furfural and primary amines. As will be seen later, however, the less reactive carbonyl of the acylfurans permits appreciable attack by amines at an alpha nuclear carbon atom, presumably giving rise to intermediate straight chain compounds which undergo recyclization with loss of water to form N-substituted acylpyrroles.

Alternatively, those furans wherein the ring is relatively electron-rich are stable toward basic reagents. In these instances, however, an electron deficiency may be created by providing an acidic medium, a deficiency which may arise by two different mechanisms depending upon whether the acid coordinates with the nucleus or with a suitable substituent. The outcome in either case would be the formation of a possibly transitory intermediate ion which is electron-poor, and therefore subject to attack by donor reagents (water, alcohol) if such are present in the reaction medium. Thus, cleavage of furfuryl alcohol to levulinic acid is catalyzed by aqueous acids, but the key step which leads to rupture is best interpreted as coordination of water (basic reagent) with an intermediate carbonium ion. As before, the extent of ring opening is dependent upon a number of factors, including the nature and number of competitive reactions which can occur. For example, the formation of levulinic acid is in competition with the resinification of furfuryl alcohol, a reaction also catalyzed by acids, but which appears not to involve ring cleavage, at least in the early stages.

In presenting this concept of cleavage it was convenient to divide furan compounds into two categories, those in which the nucleus is relatively

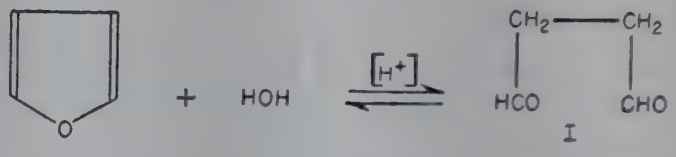
electron-poor, and those in which it is relatively electron-rich. The former types were pictured to be more or less subject to cleavage by direct attack of suitable bases, the latter to require acidic conditions in order to create a positive center in the ring which might then coordinate with a suitable donor reagent. Of course, the difference between the two categories is largely one of degree, and there is considerable overlapping. That is, under sufficiently strenuous experimental conditions it is, in all likelihood, possible to cleave any furan compound by either procedure.

Hydrolytic and Alcoholytic Fission

Acidic Medium

Cleavage of furan compounds in acidic, aqueous or alcoholic medium, is not a surprising phenomenon in view of the nuclear configuration, generally represented pictorially as a cyclic, conjugated, dienic ether. *A priori*, one might have anticipated behavior characteristics resembling those associated with vinyl ethers, and conjugated diolefins, modified to a certain extent by the stabilizing effect of resonance. To a greater or lesser degree, depending upon the type and number of substituents, such characteristics have been observed.

Harries[1] treated furan with hydrochloric acid in methanol at elevated temperature, and reported the formation of succinaldehyde, I, in the form of the acetal. Later, he[2] demonstrated the reverse reaction, whereby I was

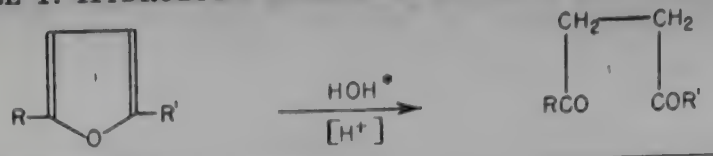


I

made to undergo cyclodehydration to give furan. From 2-methylfuran in boiling, acidic methanol, Harries[1] was able to isolate levulinaldehyde dimethyl acetal, and observed that the transformation took place with greater ease than the analogous cleavage of unsubstituted furan. This facility is also evident in the work of Wilson[3] who obtained the bis-2,4-dinitrophenylhydrazone of levulinaldehyde in 23 per cent yield when methylfuran was shaken over a period of several days with the reagent in 2*N* hydrochloric acid. The related fission of 2,5-dimethylfuran is even more readily accomplished, and with less resinification. In this instance, refluxing in aqueous acetic acid containing a small quantity of sulfuric acid gives rise to acetonylacetone, II, in 90 per cent yield[4] (see also [5]). Other examples of this

[1] Harries, *Ber.*, **31**, 37 (1898).
[2] Harries, *Ber.*, **34**, 1488 (1901).
[3] Wilson, *J. Am. Chem. Soc.*, **70**, 1313 (1948).
[4] Young and Allen, "Organic Syntheses," Collective Vol. II, p. 219, New York, John Wiley and Sons, Inc. (1948).
[5] Dietrich and Paal, *Ber.*, **20**, 1077 (1887).

Table 1. Hydrolytic Cleavage of Some Furan Types



Starting compound	R	R′	Product	Yield†	Ref.
Furan	H	H	succinaldehyde	—	1; see also 2
2-Methylfuran	H	CH_3	levulinaldehyde	low	1, 2, 3
Furfurylacetone	H	$CH_2CH_2COCH_3$	4,7-dioxoöctanal	very low	12
3-(2-Furyl)propionic acid	H	CH_2CH_2COOH	resins	—	13
2,5-Dimethylfuran	CH_3	CH_3	acetonylacetone	86–90%	4, 5
2-Methyl-5-hexylfuran	CH_3	n-C_6H_{13}	2,5-undecanedione	86%	14
2-Methyl-5-(2- (and 3-)hexenyl)-furan	CH_3	n-C_6H_{11}	7-(and 8-)undecene-2,5-dione	*ca.* 7%	15
(5-Methylfurfuryl)acetone	CH_3	$CH_2CH_2COCH_3$	2,5,8-nonanetrione	62%	16
1-(5-Methyl-2-furyl)-5-methyl-3-hexanone	CH_3	$CH_2CH_2COCH_2CH(CH_3)_2$	10-methylundecane-2,5,8-trione	—	17
3-(5-Methyl-2-furyl)propionic acid	CH_3	CH_2CH_2COOH	4,7-dioxoöctanoic acid (6-acetonyllevulinic acid)	—	18
2,5-Bis(3-oxobutyl)furan	$CH_2CH_2COCH_3$	R	2,5,8,11-dodecanetetraone	—	16
2,5-Bis(5-methyl-3-oxohexyl)-furan	$CH_2CH_2COCH_2CH(CH_3)_2$	R	2,15-dimethylhexadecane-4,7,10,13-tetraone	—	17
2,5-Furandipropionic acid	CH_2CH_2COOH	R	3,6-dioxoöctane-1,8-dicarboxylic acid (6,6′-bis-levulinic acid)	—	19; see also 20

* In most instances, an aqueous-alcoholic, or alcoholic medium was employed. The products were sometimes isolated acetals.

† In the absence of other contributing factors, the yield of product would be expected to be higher from those furans in which both α-positions are substituted, than from those possessing an α-hydrogen atom. The latter give rise to aldehydic products which would be more sensitive to destruction than the ketones derived from the former types.

type of cleavage are listed in Table 1, and the following published papers contain additional information relating to the general subject.[6, 7, 8, 9, 10, 11]



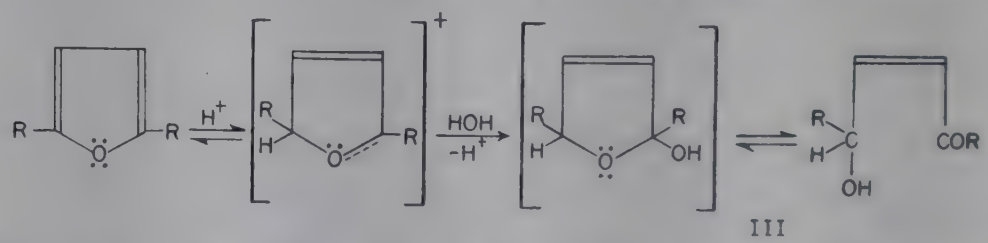
II

Acid-catalyzed hydrolysis of the nucleus resulting in the formation of saturated γ-dicarbonyl compounds as indicated above, is apparently common to many furan compounds, including furan itself, its homologs, and also various functionally substituted types, at least those wherein the functional group is remote from the ring.[b] The course of the reaction is most reasonably formulated in terms of initial attack by the acid catalyst on the furan nucleus to form an intermediate positive ion of relatively low electron density, which immediately coordinates with water and rearranges to the final product. While the steps involved have not been elucidated, it is possible to account for the results by at least two separate routes.[c]

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[b] Actually, the reaction may be common to all furan compounds, although this would be difficult to demonstrate. Certain types are very stable toward acids, and severe conditions which might promote cleavage, lead to the formation of complex resinous materials of unknown constitution. In yet other instances, functional substituents introduce a different type of reaction, although not necessarily to the exclusion of that under discussion. These factors are considered later in the text.

[c] Related to route (2) which, in essence, involves a 1,2-type addition of the elements of water, is a 1,4-type addition mechanism, and such a scheme (below) may be operative in addition to (1) or (2). While products of type III have not been re-

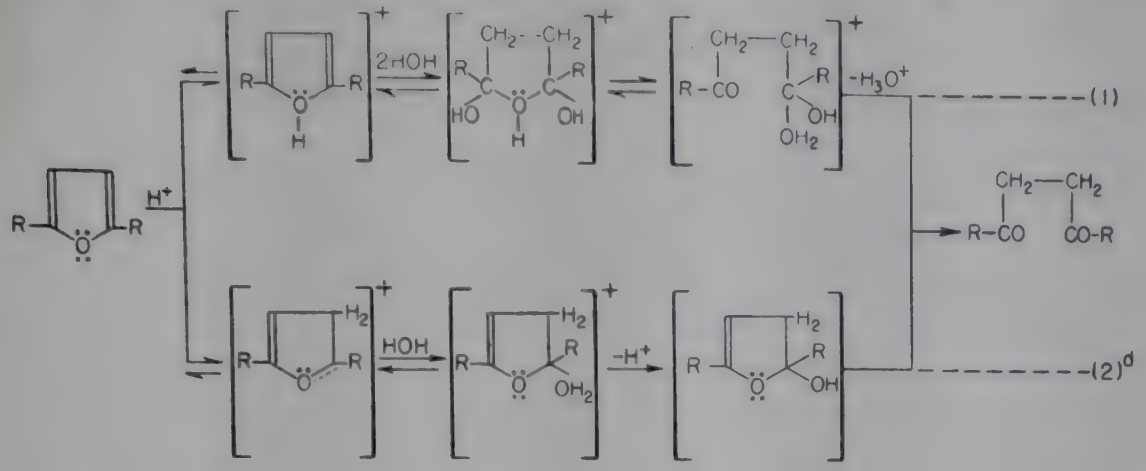


III

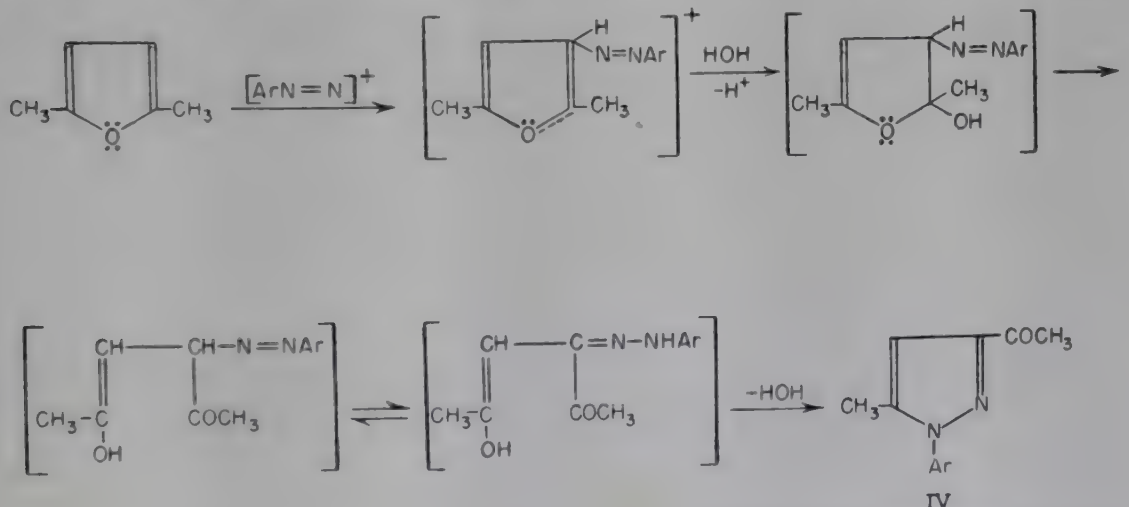
ported, it is not unlikely that such are formed as by-products. Furthermore, III might be considered to undergo prototropic rearrangement in the medium of its formation to give an intermediate, capable of ketonizing to the γ-dicarbonyl compound illustrated above. At the present time, this route looks less plausible than (1) or (2). See, however, Heilbron *et al.*, [21] (see also p. 37) for information which may have a bearing on this point.

[6] Paal, *Ber.*, **17**, 2756 (1884).
[7] Fischer and Laycock, *Ber.*, **22**, 101 (1889).
[8] Laycock, *Ann.*, **258**, 230 (1890).
[9] Reichstein, *Helv. Chim. Acta*, **13**, 345 (1930).
[10] Skrabal and Skrabal, *Z. physik. Chem.*, **A181**, 449 (1938).
[11] Kizhner, *J. Gen. Chem. U. S. S. R.*, **1**, 1212 (1931); *C. A.*, **26**, 5299 (1932).
[12] Harries and Kaiser, *Ber.*, **32**, 1320 (1899).
[13] Marckwald, *Ber.*, **20**, 2811 (1887).
[14] Hunsdiecker, *Ber.*, **75**, 447 (1942).
[15] Hunsdiecker and Wirth, *Ber.*, **75**, 460 (1942).

These are illustrated in the following diagram which, for convenience,



depicts the acid catalyst as a proton. Some of the arguments in favor of route (1) were considered earlier (p. 24). That route (2) may be operative is indicated by a reaction which was described recently by Eastman and Detert.[22] Treatment of 2,5-dimethylfuran with *p*-nitrobenzenediazonium chloride in buffered, aqueous-alcoholic solution gave rise to an intermediate product,[e] which decomposed on heating to form 1-*p*-nitrophenyl-3-acetyl-5-methylpyrazole, IV (Ar = *p*-$NO_2C_3H_4$). The reaction can be formulated in the following manner. Of course, in the reactions summarized in Table 1, the picture is complicated by competing reactions leading to resinous



IV

[d] The bond $(-\ddot{O}{=}CR)^+$ is meant to convey a resonance hybrid including $(-\ddot{O}-CR) \leftrightarrow (-\ddot{O}{=}CR)$.

[e] The coupling of furan with aryldiazonium chlorides was earlier reported by Gilman.[23] For the formation of arylfurans by reaction of furan with neutral or alkaline solutions of diazonium hydroxides, see Johnson[24] (see also p. 32).

[16] Alder and Schmidt, *Ber.*, **76**, 183 (1943).

[17] Nazarov and Nagibina, *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, **1946**, 641; *C. A.*, **42**, 7736 (1948).

tars. These may have their origin in the starting furan compound, the cleavage products, or possibly a combination of these. It is worthy of note that where one or both R groups is a hydrogen atom, the yield of simple product is generally poor, attributable in all likelihood to its reactive aldehydic nature.

The ease of formation of ionic intermediates of the type illustrated above (p. 643) would obviously be dependent upon the ability of the starting furan compound to act as an electron donor. It is not surprising, therefore, to find that furans possessing substituents which have an electron-withdrawing effect, namely those with substituents which are *meta*-orienting in the benzene series, are more resistant to acid-catalyzed cleavage than compounds of the type listed in Table 1. This is attested by the experience of many investigators, summed up admirably by Gilman and Young,[25] and is understandable in terms of the effect of such substituents in decreasing the electron density in the ring.[f] This effect is illustrated specifically for the isomeric mononitro compounds:



Nitrofurans, and the furancarboxylic acids and esters are, in fact, notably resistant to attack by aqueous acids. Qualitatively, furfural and the acylfurans are somewhat less resistant although with the former, kinetic studies have revealed that, even here, comparatively severe conditions are required to bring about extensive destruction (p. 295). In part, this destruction may be a consequence of ring cleavage of the type which has been discussed, but it is not unlikely that competing reactions involving the aldehyde group

[f] This same effect on the relative tendency of furan compounds to act as electron donors is also apparent in connection with their use in the diene synthesis. Furans carrying electron-withdrawing substituents are less dienic in character than, for example, furan and its homologs, and they fail to form adducts with maleic anhydride (see p. 61). It should be noted, however, that the decreased electron density in the nucleus of these types, explains their susceptibility to attack by basic (donor) reagents (see p. 658).

[18] Robinson and Todd, *J. Chem. Soc.*, **1939**, 1743.

[19] Sherlin, Berlin, Serebrennikova and Rabinovich, *J. Gen. Chem. U. S. S. R.*, **8**, 7 (1938); *C. A.*, **32**, 5397 (1938).

[20] Asahina and Fujita, *J. Pharm. Soc. Japan*, **461**, 583 (1920); *C. A.*, **14**, 3227 (1920).

[21] Heilbron, Jones, Smith and Weedon, *J. Chem. Soc.*, **1946**, 54.

[22] Eastman and Detert, *J. Am. Chem. Soc.*, **70**, 962 (1948).

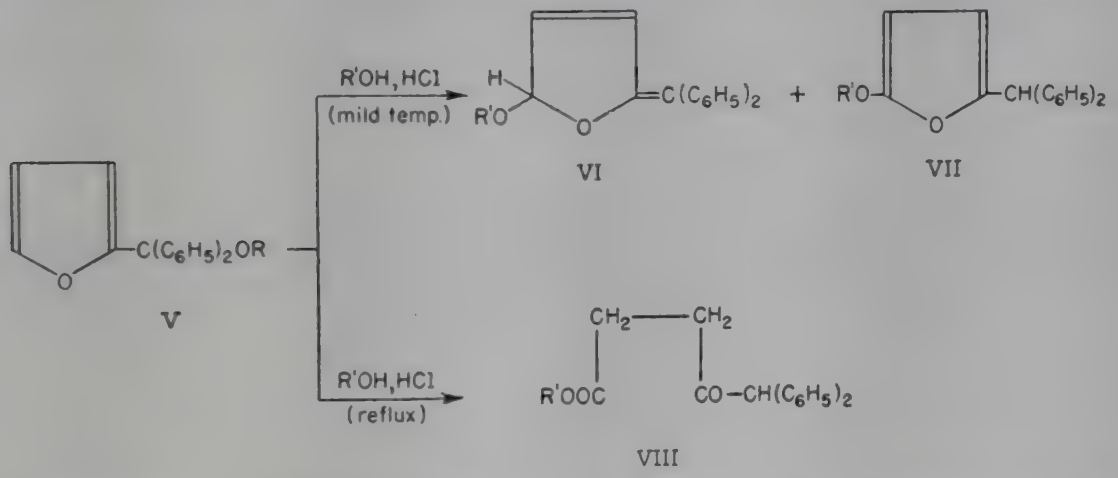
[23] Gilman, Wooley and Vander Wal, *Proc. Iowa Acad. Sci.*, **39**, 176 (1932); *C. A.*, **28**, 6714 (1934).

[24] Johnson, *J. Chem. Soc.*, **1946**, 895.

[25] Gilman and Young, *Rec. trav. chim.*, **51**, 761 (1932).

are of equal, or perhaps greater importance. Unfortunately, this subject has not received the attention which it deserves, and further comment must await the outcome of future investigations.

That the course of reaction can be materially altered by involvement of a suitable substituent is indicated by the information now available on the action of aqueous and alcoholic acids on various 2-furylcarbinols and their ethers. For example, when Ushakov and Kucherov[26] treated diphenylfurylcarbinol (V, R = H) with hydrochloric acid in methanol, and in ethanol, they observed a slight evolution of heat followed by precipitation of 2-(diphenylmethylene)-5-alkoxy-2,5-dihydrofuran (VI; R′ = CH_3, and C_2H_5, respectively). When the methyl ether of V (R = CH_3), in acetic anhydride, was similarly exposed to methanolic hydrogen chloride, 2-(diphenylmethyl)-5-methoxyfuran, VII (R′ = CH_3), was obtained as a precipitate, and VI (R′ = CH_3) was found in the mother liquor. Under reflux conditions, reaction proceeds further, so that by refluxing a solution of V (R = H) in methanol containing a little hydrochloric acid, 5,5-diphenyllevulinic ester, VIII, was obtained. These reactions are summarized in the following dia-



gram. Ushakov and Kucherov[26] concluded that the transformation of V into VIII proceeds in three stages: anionotropic change to VI, followed by prototropic rearrangement to VII, and subsequent hydrolysis to VIII. They were successful in effecting similar conversions with several alkylfurylcarbinols (see also [26a]) which gave rise to the appropriate 5-alkyllevulinic acids, confirming thereby the observations of Chichibabin[27] that the reaction offers a general method for the synthesis of γ-keto acids.

[26] Ushakov and Kucherov, *J. Gen. Chem. U. S. S. R.*, **14**, 1080 (1944); *C. A.*, **40**, 7185 (1946).

[26a] Kucherov, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20**, 1885 (1950); *C. A.*, **45**, 2928 (1951).

[27] Chichibabin, *Congr. chim. ind. Compl. rend.*, **11**, 563 (1932); *C. A.*, **26**, 3778 (1932).

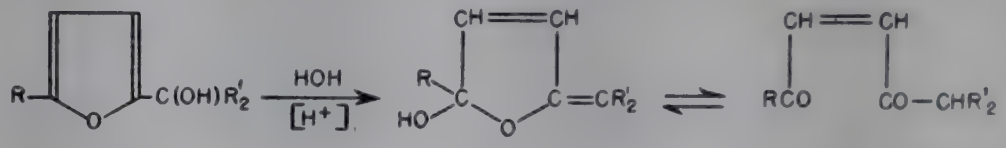
[27a] Gilman, Franz, Hewlett and Wright, *J. Am. Chem. Soc.*, **72**, 3 (1950).

Certainly, it appears to be common to all 2-furylcarbinols which are unsubstituted in the 5-position of the nucleus[g] (see Table 2).

The simplest of these, furfuryl alcohol, gives rise to levulinic acid itself, X (see also p. 224). In the light of what has gone before and of other considerations yet to be discussed, it is believed that this transformation proceeds by way of the resonating carbonium ion, A, arising by attack of a proton on the hydroxyl group and subsequent loss of the elements of water. In aqueous medium, A would be subject to recoordination with water in two different ways, (1) to regenerate furfuryl alcohol and (2) in a manner leading to the formation of 5-hydroxy-2-methylene-2,5-dihydrofuran, B[h] (compare with VI, above; see also relation of B to the postulated intermediate involved in the conversion of furfuryl chloride into 5-methyl-2-

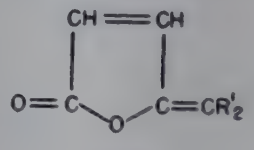
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[g] Comparatively little is known with regard to the behavior of 5-substituted 2-furylcarbinols when exposed to acidic reagents in aqueous or alcoholic medium. It will be apparent, however, that a substituent (e.g., CH_3) in this location would obviate rearrangement of the type VI → VII postulated by Ushakov and Kucherov.[26] Accordingly, one might expect to find products of type IX or IX A. In this connec-



IX IX A

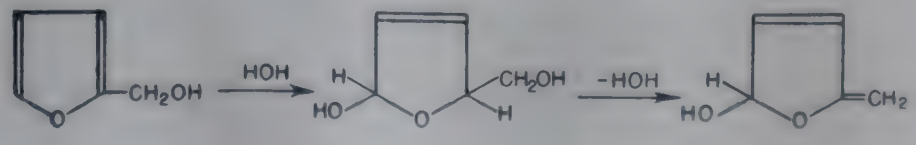
tion, Gilman and his associates[27a]; (see also p. 101) have recently called attention to the conversion of 5-halo-2-furylcarbinols (e.g., R = Br) under acidic conditions to substituted crotonolactones, IX B. This reaction occurs with such facility that



IX B

it is impossible to isolate the expected tertiary alcohol when 5-halo-2-furoic ester is placed in reaction with the Grignard reagent. Attempted hydrolysis of the resulting Grignard complex gives IX B directly.

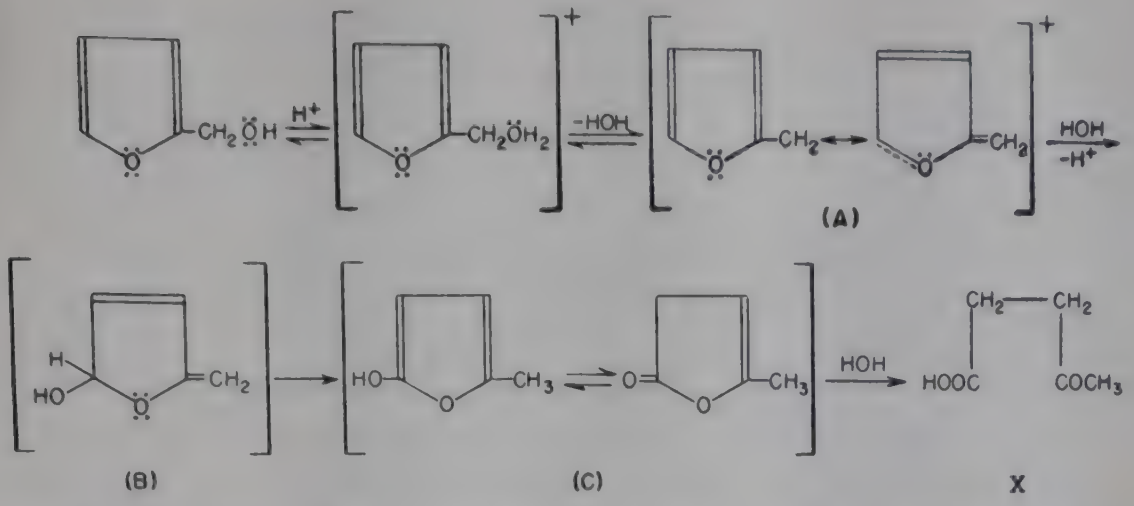
[h] It will be observed that B is a cyclic hemiacetal of the enol form of 3-acetylacrolein. Derivatives of the latter have actually been obtained from solutions of furfuryl alcohol in aqueous or alcoholic medium.[28] Leger and Hibbert[29] also postulated B as an intermediate, but suggested its formation by way of a 1,4-type addition of water to the nucleus, and subsequent dehydration as indicated below:



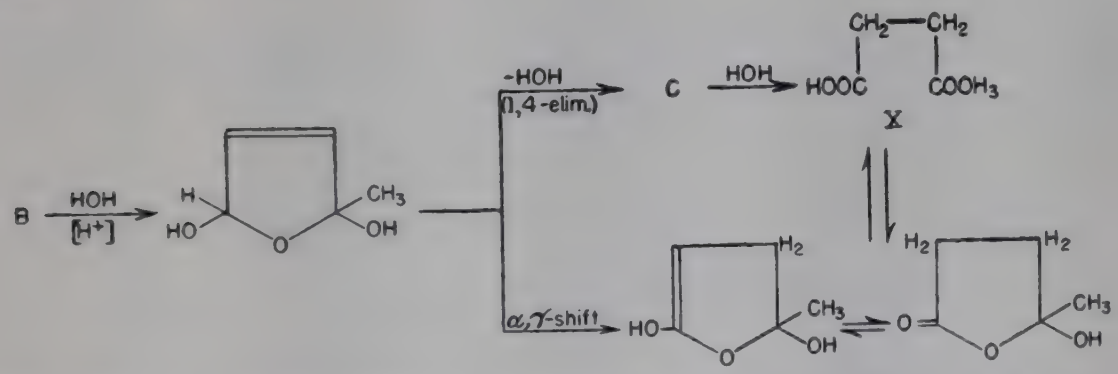
(B)

[28] The Quaker Oats Company, unpublished work.

[29] Leger and Hibbert, *Can. J. Research*, **16B**, 68 (1938).



furonitrile (p. 551). The transformation of B into X[i] is indicated to go forward by way of α-angelica lactone, C. The latter may arise by prototropic rearrangement (α, ϵ) of B as indicated by the work of Ushakov and Kucherov[26] on diphenylfurylcarbinol, or possibly by an addition-elimination sequence involving the elements of water as outlined below. On the other hand, the postulated addition product of water to B might be supposed to give X (as the cyclic hemiacylal) directly by α, γ-rearrangement of a proton.



At this point it is necessary to account for the findings of Pummerer and his associates[31, 32] (see also [33]). When furfuryl alcohol, or its methyl ether, was refluxed with dilute methanolic hydrogen chloride, these workers obtained methyl levulinate and, in addition a compound $C_8H_{16}O_4$, easily convertible into levulinic acid (ester) by the further action of acid. They formulated this product as an ether-acetal derivative, XI, of 5-hydroxy-levulinaldehyde, and concluded that XI was intermediate in the conversion of furfuryl alcohol to levulinic acid; that in acidic medium, XI undergoes

[i] A different mechanism to account for levulinic acid from intermediates related to B, and to acetylacrolein, has been formulated by Isbell.[30] This involves hydrolytic cleavage of B to 3-acetylacrolein followed by a series of consecutive electron displacements catalyzed by acids.

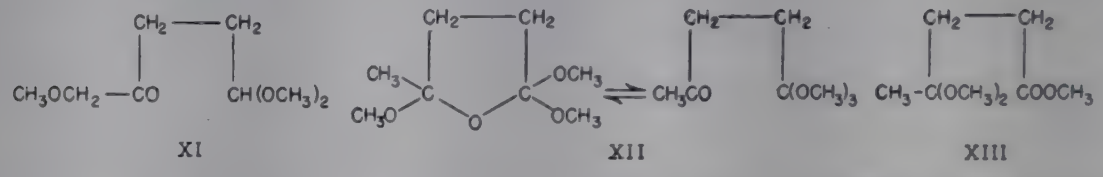
[30] Isbell, *J. Research Natl. Bur. Standards*, **32**, 45 (1944).

[31] Pummerer and Gump, *Ber.*, **56**, 999 (1923).

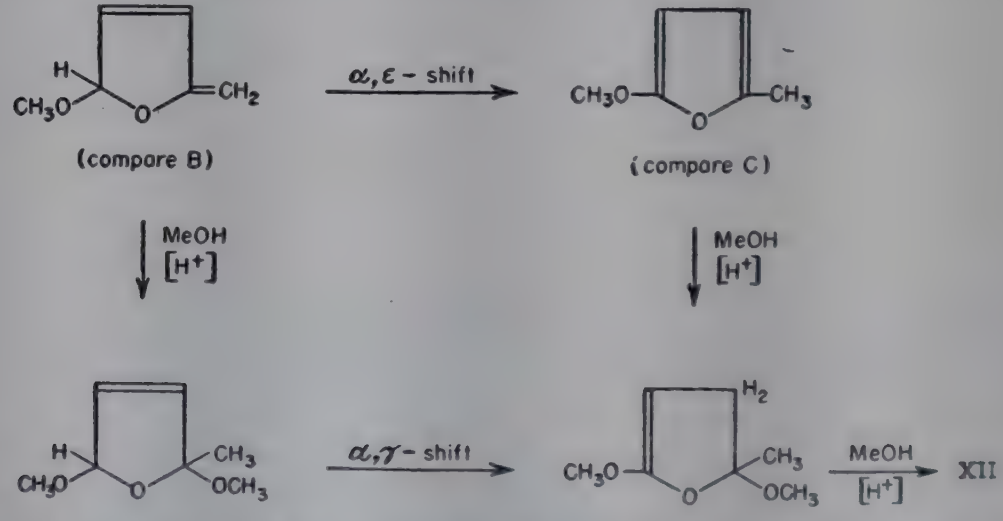
[32] Pummerer, Guyot and Birkhofer, *Ber.*, **68**, 480 (1935).

[33] Deriaz, Stacey, Teece and Wiggins, *J. Chem. Soc.*, **1949**, 1222.

some sort of intramolecular oxidation-reduction, whereby the aldehyde (acetal) group is oxidized to carboxyl at the expense of the hydroxyl (ether) group. The improbability of such a dismutation was the basis for the challenge of Pummerer's explanation by Leger and Hibbert.[29] XI is, of course, a product to be expected if furfuryl alcohol were cleaved in a manner similar to that discussed earlier for the fission of furan and its homologs (alcoholysis of the ether linkage of the nucleus), and it is possible that XI is actually formed, to a certain extent, as a by-product. However, the major course of reaction is believed to be as illustrated above (p. 647), and in accordance with this view, it is suggested that Pummerer's intermediate was actually the levulinic ortho-ester, XII[j] (shown in open and cyclic forms), or possibly the isomeric methyl acetal, XIII, of methyl levulinate. More readily than XI, these structures explain the facile conversion to levulinic acid observed by Pummerer,[31] and also the fact that catalytic reduction[k] and subsequent heating with 0.5*N* sulfuric acid is reported[32] to give rise to γ-valerolactone.

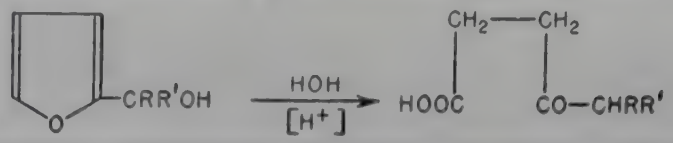


[j] Formation of XII could be explained from an intermediate such as 5-methoxy-2-methylene-2,5-dihydrofuran as outlined below:



[k] Using a platinum catalyst, slightly more than one mole of hydrogen was absorbed over a period of *three weeks*. Distillation permitted isolation of a product $C_8H_{18}O_4$ (C, H analyses) which was stable toward cold and hot alkali, and which gave negative Fehling's and fuchsin tests. On standing in 0.5*N* sulfuric acid at room temperature for *eight days*, this product was converted into a compound, $C_6H_{12}O_3$ (C, H analyses) which reduced Fehling's solution and ammoniacal silver solution in the cold. It failed to redden fuchsin reagent, failed to give crystalline derivatives with semicarbazide and phenylhydrazine, but produced a derivative, $C_{18}H_{18}N_8O_9$ (C, H, N analyses) with 2,4-dinitrophenylhydrazine.[32] It is not immediately apparent how this behavior can be reconciled with any of the structures (XI, XII and XIII) which have been proposed. Repetition of this work would appear to be very much in order.

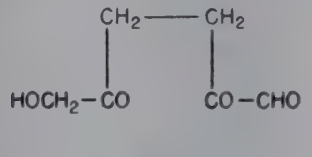
Table 2. Conversion of 2-Furylcarbinols to Levulinic Acids



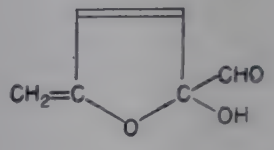
Starting compound	R	R′	Product*	Yield	Ref.
Furfuryl alcohol	H	H	levulinic acid	62–64%	34; see also 31, 35, 27, 32, 37
Methylfurylcarbinol	H	CH_3	4-oxohexanoic acid (5-methyl-levulinic acid)	60%	27, 26, 36
Ethylfurylcarbinol	H	C_2H_5	4-oxoheptanoic acid		27
Isopropylfurylcarbinol	H	*i*-C_3H_7	6-methyl-4-oxoheptanoic acid	53.5%	26
Isobutylfurylcarbinol	H	*i*-C_4H_9	7-methyl-4-oxoöctanoic acid	51%	26, 26a
n-Butylfurylcarbinol	H	*n*-C_4H_9	4-oxononanoic acid	45%	26a
Benzylfurylcarbinol	H	$C_6H_5CH_2$	6-phenyl-4-oxohexanoic acid	—	26
Phenethylfurylcarbinol	H	$C_6H_5CH_2CH_2$	7-phenyl-4-oxoheptanoic acid	49%	26a
Cyclopentylfurylcarbinol	H	C_5H_9	5-cyclopentyllevulinic acid	—	38
Cyclohexylfurylcarbinol	H	C_6H_{11}	5-cyclohexyllevulinic acid	*ca.* 80%	27
Phenylfurylcarbinol	H	C_6H_5	5-phenyllevulinic acid	*ca.* 80%	27
Diphenylfurylcarbinol	C_6H_5	C_6H_5	5,5-diphenyllevulinic acid	—	26

* In an alcoholic medium, esters are obtained instead of the acids.

In connection with the conversion of 5-(hydroxymethyl)furfural to levulinic and formic acids it is tempting to consider that the initial step involves hydrolytic cleavage of the aldehyde group to form furfuryl alcohol and formic acid. Pummerer[31, 32] rejected this possibility on the grounds that the yield of levulinic acid from the aldehyde is substantially greater[33, 35] (see also [40]) than is obtainable from furfuryl alcohol under similar conditions. Accordingly, he formulated the conversion as proceeding by way of 2,5-dioxo-6-hydroxyhexanal, XIV, the relationship of which to XI will be readily apparent, and suggested that XIV was cleaved hydrolytically to formic acid and 5-hydroxylevulinaldehyde, the latter as before, undergoing dismutation to levulinic acid. An alternative mechanism was later offered by Isbell[30] who proposes 5-methylene-2-hydroxy-2,5-dihydrofurfural, XV (compare B, above) as an intermediate. This is in accord with the scheme presented above (page 647) for the formation of levulinic acid from furfuryl alcohol; initiation of reaction by attack on the hydroxyl group rather than on the nucleus.

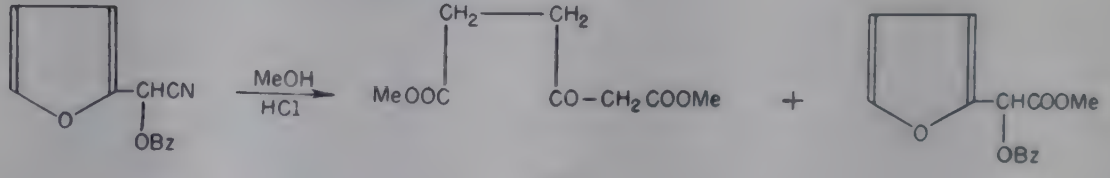


XIV



XV

Irrespective of the mechanism, it is apparent that the net effect of the action of aqueous acids on the miscellaneous 2-furylcarbinols (Table 2), including 5-(hydroxymethyl)furfural, is to replace the hydroxyl group by hydrogen and to transform the nucleus into a γ-ketobutyric residue, $—COCH_2CH_2COOH$. Therefore it is not surprising to note that Lukeš[41] obtained 3-ketoadipic ester, XVI, in addition to O-benzoyl-2-furylglycollic ester, XVII, when the benzoyl derivative of furfural cyanohydrin was treated with methanolic hydrogen chloride.



XVI XVII

[34] Berkenheim and Dankova, *J. Gen. Chem. U. S. S. R.*, **9**, 924 (1939); *C. A.*, **34**, 368 (1940).

[35] Teunissen, *Rec. trav. chim.*, **50**, 1 (1931).

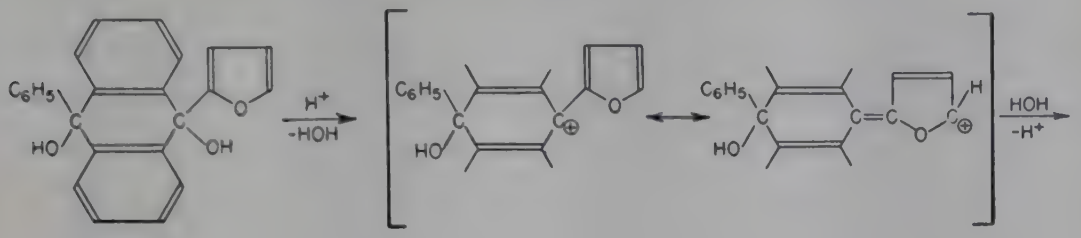
[36] Moffatt, Newberry and Webster, *J. Chem. Soc.*, **1946**, 451.

[37] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 19 (1942); *C. A.*, **44**, 8859 (1950).

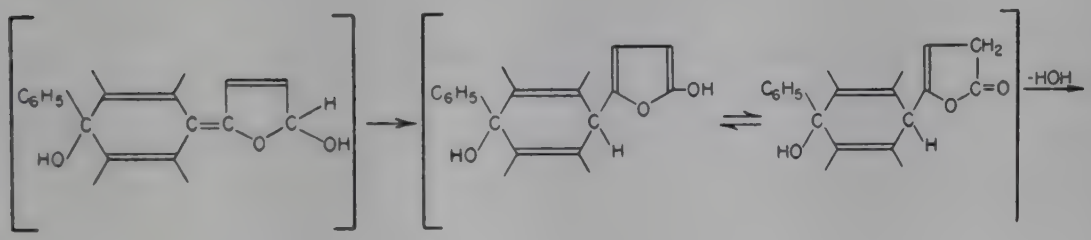
[38] Katsnel'son and Kondakova, *Compt. rend. acad. sci. U. R. S. S.*, **17**, 367 (1937); *C. A.*, **32**, 7022 (1938).

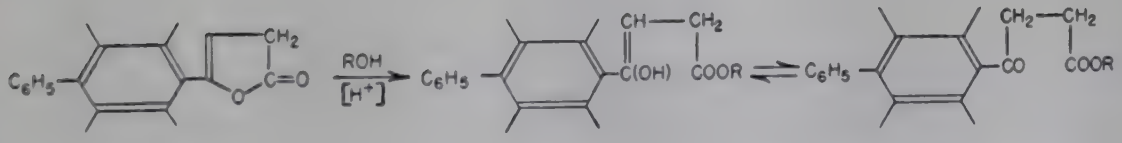
[39] Teunissen, *Rec. trav. chim.*, **49**, 784 (1930).

The interesting observations of Étienne and Brisson[42, 43, 44] are subject to explanation in similar terms. The *ms*-furylquinols of anthracene with which they worked behaved abnormally with alcohols in the presence of hydrochloric acid. For example, 9-furyl-10-phenyl-9,10-dihydroxy-9,10-dihydroanthracene, XVIII (p. 259), was converted into the carboxylic ester, XX,[1] instead of the expected quinol ether. In accordance with the previous discussion it can be seen that XVIII has reacted as a 2-furylcarbinol. A plausible course is outlined below; the proposed intermediate lactone, XIX, has actually been isolated under slightly modified conditions (see p. 172). Failure of the monoquinol, 9-furyl-10-phenyl-9-hydroxy-9,10-dihy-



XVIII





XIX XX

[1] Étienne and Brisson[42, 43] preferred to represent these esters (XX) in the enol form rather than the tautomeric 4-oxobutanoic form, mainly because they failed to give carbonyl derivatives. It is possible that they might be more properly assigned a pseudo-ester structure, like the levulinic pseudo-esters derived from α-angelica lactone (see Langlois and Wolff[45]).

[40] Haworth and Wiggins, British Pat. 591,858 (1947); *C. A.*, **42,** 1317 (1948).

[41] Lukeš, Kastner, Gut and Herben, *Collection Czechoslov. Chem. Communs.*, **12,** 647 (1947); *C. A.*, **42,** 5852 (1948).

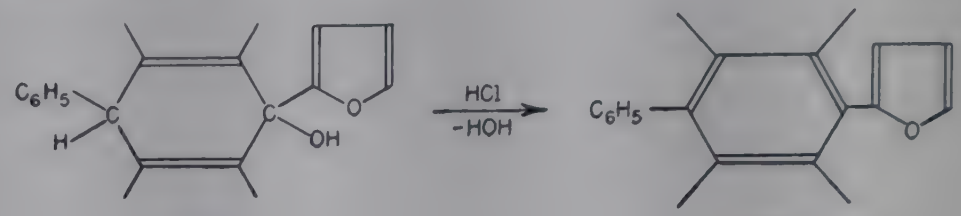
[42] Étienne and Brisson, *Compt. rend.*, **224,** 1775 (1947).

[43] Étienne and Brisson, *Compt. rend.*, **227,** 208, 288 (1948).

[44] Brisson, *Compt. rend.*, **227,** 1103 (1948).

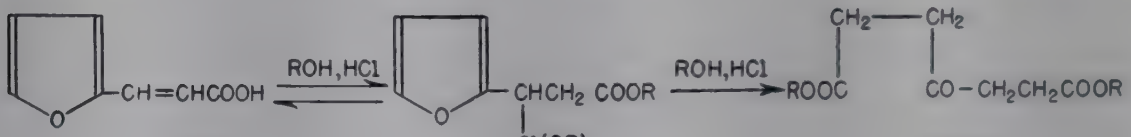
[45] Langlois and Wolff, *J. Am. Chem. Soc.*, **70,** 2624 (1948).

droanthracene, XXI, to exhibit this behavior is not surprising, since by a simple dehydration it can revert from the dihydro structure to the more stable anthracene system. In this way, XXI gives rise to 2-(10-phenyl-9-anthryl)furan, XXII.



XXI XXII

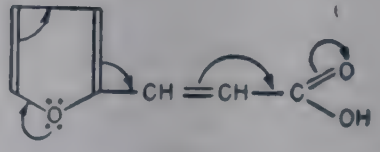
Also related to these reactions of the 2-furylcarbinols is a transformation first noted by Marckwald,[13] whereby 4-ketopimelic ester, XXIV, is obtained by alcoholysis of 3-(2-furyl)acrylic acid, XXIII, in the presence of hydrochloric acid or dry hydrogen chloride. *A priori*, the carboxyl group of XXIII might have been expected to confer, on the nucleus, a considerable degree of acid-stability,[m] similar to that observed in the case of furoic acid (see discussion of the effect of electron-withdrawing substituents on the tendency of acidic reagents to attack the nucleus (p. 644)). Yet XXIII is largely cleaved by alcoholic hydrogen chloride under conditions which effect only esterification of furoic acid. Accordingly, it would appear that, in the former instance, there is some initial reaction which prepares the way for the observed result. It is likely that this preliminary step involves the addition of hydrogen chloride, or perhaps the elements of alcohol to the double bond of the side chain to form D, a 2-furylcarbinol type and,



XXIII (D) XXIV

therefore, subject to similar cleavage. Support for D as an intermediate is seen in the fact that 2-(2-nitrovinyl)furan, XXV,[46] and its hydrated relative,

[m] One effect of the carboxyl group of XXIII, acting through the extended conjugated system, would be to lower the electron density in the furan nucleus. That this

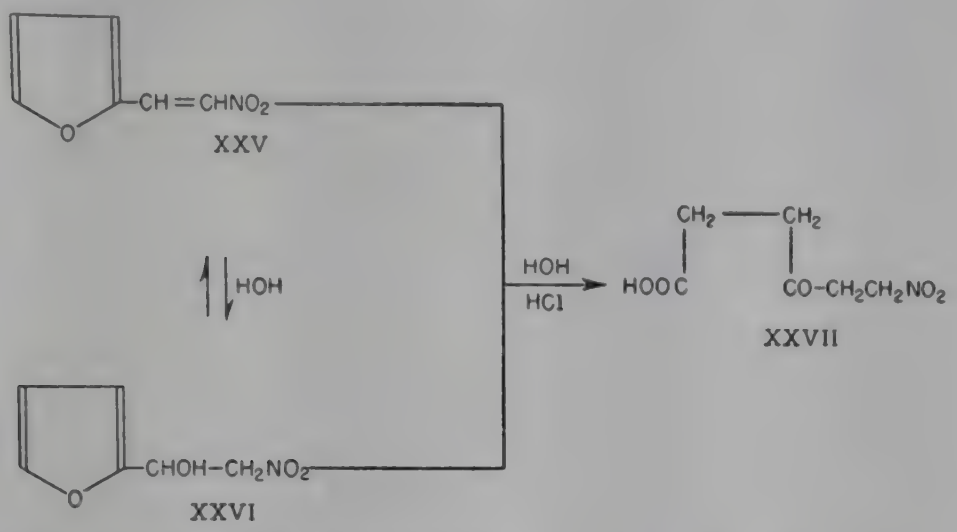


XXIII

effect actually exists is indicated by the failure of XXIII to form an adduct with maleic anhydride whereas the related 3-(2-furyl)propionic acid in which the carboxyl group can have no similar effect, can add this reagent to the nucleus (see p. 61).

[46] Thiele and Landers, *Ann.*, **369**, 300 (1909).

1-(2-furyl)-2-nitro-1-ethanol, XXVI,[47] behave similarly on heating with aqueous hydrochloric acid, giving rise to a common product, 6-nitro-4-oxohexanoic acid, XXVII.



Similar conversions with furfurylideneacetone, furfurylideneacetophenone and related types, XXVIII, are listed in Table 3. These give rise to 7-R-4,7-dioxoheptanoic acids, XXIX, which saturated γ-dicarbonyl compounds are subject to recyclization, with loss of water, to form 3-(5-R-2-furyl)propionic acids, XXX.[n] The latter are representative of those furan types listed in Table 1, hence it is not unlikely that in hot, aqueous, acidic medium, XXIX and XXX are in equilibrium (see p. 591), that both products are present in the reaction mixture (see [61]), the relative proportions varying with the

[n] The reaction also offers a route to similarly substituted pyrryl- and thienylpropionic acids, since XXIX can be cyclized in the presence of ammonium acetate or phosphorus pentasulfide to obtain the appropriate heterocycle. With phosphorus pentoxide, closure to XXX (R = C_6H_5) has been accomplished in 88 per cent yield.[66, 65]

[47] Kanao, *J. Pharm. Soc. Japan*, **550**, 1019 (1927); *C. A.*, **22**, 1588 (1928).

[48] Singleton (to Robertson Co.), U. S. Pat. 2,436,532 (1948); *C. A.*, **42**, 5048 (1948).

[49] Deutsche Hydrierwerke A.-G., French Pat. 901,977 (1945).

[50] Marckwald, *Ber.*, **21**, 1398 (1888).

[51] Volhard, *Ann.*, **253**, 235 (1889).

[52] Hachihama, Imoto and Asawo, *J. Soc. Chem. Ind. Japan, Suppl. binding*, **45**, 406 (1942); *C. A.*, **44**, 8859 (1950).

[53] Hachihama, Imoto and Taniyama, *J. Soc. Chem. Ind. Japan*, **46**, 119B (1943); *C. A.*, **44**, 8859 (1950).

[54] Yahama *et al.* (to Teikoku Seni K. K.) Japanese Pat. 172,472 (1946); *C. A.*, **43**, 6866 (1949).

[55] Likhosherstov, Zeberg and Karitskaya, *Zhur. Obshchei Khim. J. Gen. Chem.*, **20**, 635 (1950); *C. A.*, **44**, 7823 (1950).

[56] Carter, *J. Am. Chem. Soc.*, **50**, 2299 (1928).

[57] Kehrer and Hofacker, *Ann.*, **294**, 165 (1897)

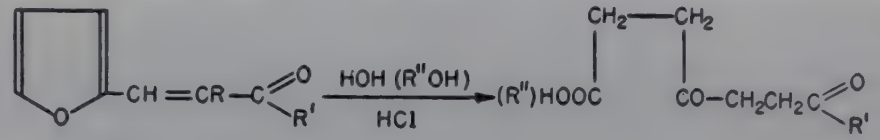
[58] Kehrer and Igler, *Ber.*, **32**, 1176 (1899).

[59] Breusch and Ulusoy, *Rev. faculté sci. univ. Istanbul*, **13A**, 51, (1948); *C. A.*, **42**, 5850 (1948).

[60] Fujita, *J. Pharm. Soc. Japan*, **493**, 148 (1923); *C. A.*, **17**, 3030 (1923).

[61] Robinson, *J. Chem. Soc.*, **1938**, 1390.

TABLE 3. HYDROLYTIC (ALCOHOLYTIC) CLEAVAGE OF FURYLACRYLIC ACID, FURYLALKENONES AND RELATED FURAN TYPES



Starting compound	R	R′	Product	Yield†	Ref.
3-(2-Furyl)acrylic acid	H	OH	3-oxo-1,5-pentanedicarboxylic acid (γ-ketopimelic acid)	*ca.* quant.	48, 49, 13, 50, 51, 27, 52, 53, 54, 55
3-(2-Furyl)-2-ethylacrylic acid	C_2H_5	OH	3-oxo-1,5-heptanedicarboxylic acid	96%	56
δ-Furfurylidenelevulinic acid	H	CH_2CH_2COOH	3,6-dioxo-1,8-octanedicarboxylic acid* (δ, δ′-bilevulinic acid)	low	57
Furfurylideneacetone	H	CH_3	4,7-dioxoöctanoic acid (δ-acetonyllevulinic acid)	26%	14, 58, 59; see also 60
Furfurylidenemethyl ethyl ketone	H	C_2H_5	4,7-dioxononanoic acid	—	14, 59
Furfurylidenemethyl propyl ketone	H	*n*-C_3H_7	4,7-dioxodecanoic acid	—	59
Furfurylidenemethyl butyl ketone	H	*n*-C_4H_9	4,7-dioxoundecanoic acid	—	59
Furfurylidenemethyl *i*-butyl ketone	H	*i*-C_4H_9	4,7-dioxo-9-methyldecanoic acid	—	59
Furfurylidenemethyl pentyl ketone	H	*n*-C_5H_{11}	4,7-dioxododecanoic acid	—	59
Furfurylideneacetophenone	H	C_6H_5	4,7-dioxo-7-phenylheptanoic acid (δ-phenacyllevulinic acid)	55–60%	61, 58, 62; see also 63
p-Methyl-furfurylideneacetophenone	H	*p*-$CH_3C_6H_4$	4,7-dioxo-7-*p*-tolylheptanoic acid	61%	64
p-Ethyl-furfurylideneacetophenone	H	*p*-$C_2H_5C_6H_4$	4,7-dioxo-7-*p*-ethylphenylheptanoic acid	60%	64
p-Isopropyl-furfurylideneacetophenone	H	*p*-(*i*-C_3H_7)C_6H_4	4,7-dioxo-7-*p*-isopropylphenylheptanoic acid	50%	64
p-*sec*.-Pentyl-furfurylideneacetophenone	H	*p*-(*sec*.-C_5H_{11})C_6H_4	4,7-dioxo-7-*p*-*sec*.-pentylphenylheptanoic acid	not isolated†	64
p-Cyclohexyl-furfurylideneacetophenone	H	*p*-(C_6H_{11})C_6H_4	4,7-dioxo-7-*p*-cyclohexylphenylheptanoic acid	32%	64
p-Phenyl-furfurylideneacetophenone	H	*p*-(C_6H_5)C_6H_4	4,7-dioxo-7-*p*-xenylheptanoic acid	20%	64

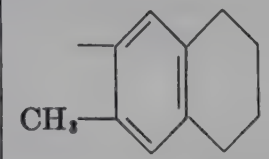
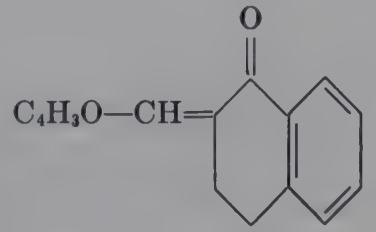
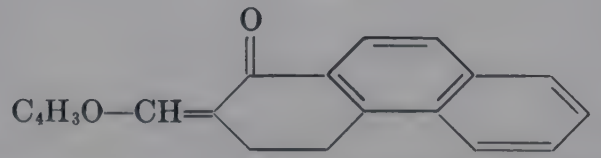
m-Methoxy-furfurylideneacetophenone	H	*m*-$(OCH_3)C_6H_4$	4,7-dioxo-7-*m*-methoxyphenylheptanoic acid	—	65
p-Methoxy-furfurylideneacetophenone	H	*p*-$(OCH_3)C_6H_4$	4,7-dioxo-7-*p*-methoxyphenylheptanoic acid	50–55%	66
Furfurylidene-(2-hydroxy-4-methoxyacetophenone)	H	2,4-$(OH)(OCH_3)C_6H_3$	4,7-dioxo-7-(2-hydroxy-4-methoxyphenyl)-heptanoic acid	—	67, 68; see also p. 472
Furfurylidene-(2-hydroxy-5-methoxyacetophenone)	H	2,5-$(OH)(OCH_3)C_6H_3$	4,7-dioxo-7-(2-hydroxy-5-methoxyphenyl)-heptanoic acid	—	67
Furfurylideneacetoveratrone	H	3,4-$(OCH_3)_2C_6H_3$	4,7-dioxo-7-veratrylheptanoic acid	poor	61
Furfurylidene-2-hydroxy-3,4-dimethoxyacetophenone	H	2,3,4-$(OH)(OCH_3)_2C_6H_2$	4,7-dioxo-7-(2-hydroxy-3,4-dimethoxyphenyl)heptanoic acid	—	68
Furfurylidene-2-hydroxy-4,5-dimethoxyacetophenone	H	2,4,5-$(OH)(OCH_3)_2C_6H_2$	4,7-dioxo-7-(2-hydroxy-4,5-dimethoxyphenyl)heptanoic acid	—	68
Furfurylidene-(3-methyl-4-methoxy-6-chloroacetophenone)	H	3,4,6-$(CH_3)(OCH_3)$-$(Cl)C_6H_2$	‡	—	65
Furfurylidenepropiophenone	CH_3	C_6H_5	‡	—	64
Furfurylidene-2-acetonaphthone	H	2-$C_{10}H_7$	4,7-dioxo-7-(2-naphthyl)heptanoic acid	63%	61
Furfurylidene-(4-methoxy-1-acetonaphthone)	H	1-$C_{10}H_6$(4-OCH_3)	4,7-dioxo-7-(4-methoxy-1-naphthyl)heptanoic acid	not isolated†	64
Furfurylidene-(6-methoxy-2-acetonaphthone)	H	2-$C_{10}H_6$(6-OCH_3)	4,7-dioxo-7-(6-methoxy-2-naphthyl)-heptanoic acid	54%	61
ω-Furfurylidene-(3-methyl-5,6,7,8-tetrahydro-2-acetonaphthone)	H		4,7-dioxo-7-(3-methyl-5,6,7,8-tetrahydro-2-naphthyl)heptanoic acid	—	69

TABLE 3.—*Concluded*

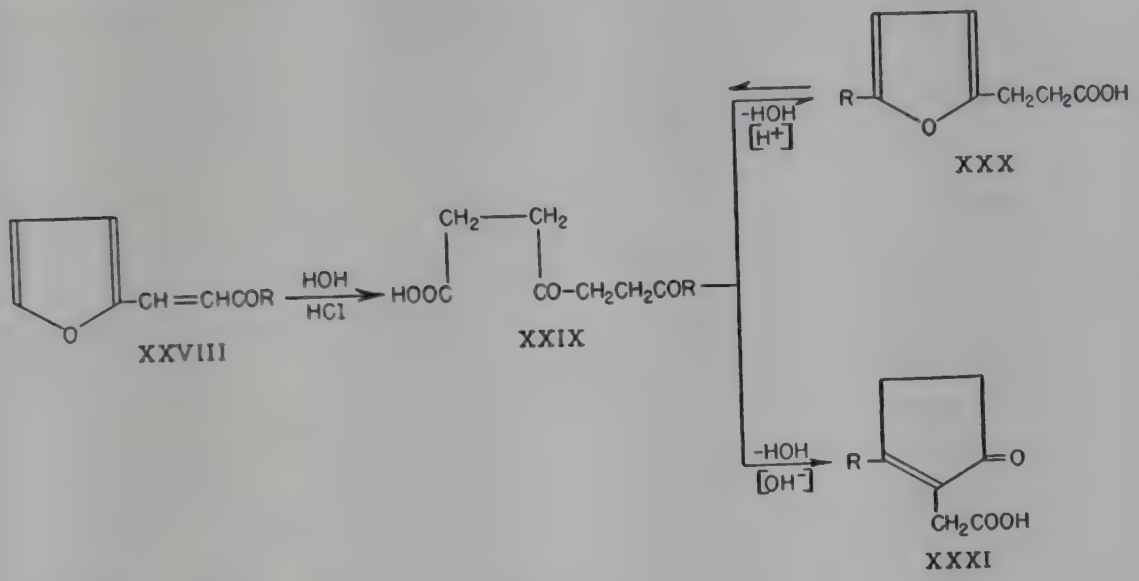
Starting compound	Structure	Product	Yield†	Ref.
Furfurylidene-α-tetralone (2-furfurylidene-3,4-dihydro-1(2*H*)-naphthalenone)		δ-(1-oxo-1,2,3,4-tetrahydro-2-naphthyl)-levulinic acid	16%	64
2-Furfurylidene-3,4-dihydro-1(2*H*)-phenanthrenone		δ-(1-oxo-1,2,3,4-tetrahydro-2-phenanthryl)levulinic acid	53%	64

* Also obtainable by hydrolytic cleavage of 2,5-furandipropionic acid, $HOOCCH_2CH_2—C_4H_2O—CH_2CH_2COOH$. Others among the listed products were similarly obtained from $R—C_4H_2O—CH_2CH_2COOH$ types (see Table 1; see also p. 591).

† The cleavage products were not isolated; they were immediately cyclized to substituted cyclopentenones by the action of alkali (see text).

‡ The conditions of acid-catalyzed cleavage of the original furan compound were such as to promote recyclization of the initial γ-dicarbonyl product to a new furan product of the type: $R—C_4H_2O—CH_2CH_2COOH$ (see text).

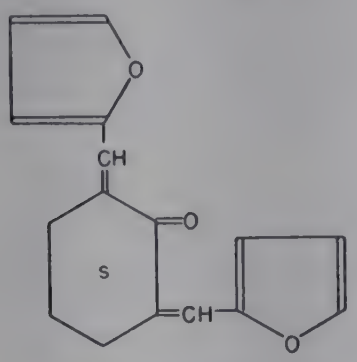
experimental conditions, including the method of isolation, and perhaps, the nature of R. In most examples, XXIX is the sole reported product, but in a few experiments, XXX was the only simple product which was isolated (see Table 3). Accordingly, even if resinous by-products are neglected, the yield of XXIX may not be truly indicative of the extent of cleavage of the original furan compound (XXVIII). It is of interest to point out that Robinson[61] (see also [64]) has employed the cleavage reaction in studies related to the syntheses of the sex hormones. Compounds of type XXIX are potentially useful intermediates in these syntheses since they undergo intramolecular condensation under alkaline conditions to form substituted cyclopentenones, XXXI:



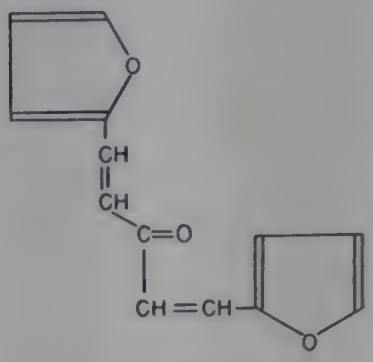
From the data in Table 3 it is apparent that fission of the type illustrated is common to furans possessing the group —CH=CR—CO— attached to the nucleus at an alpha position, and which are unsubstituted[g] at the other α-position. This would appear to be true even when the conjugated alkenone system is part of an alicyclic ring. Thus, Turner[64] has shown that the reaction is applicable to furfurylidene-α-tetralone, and to 2-furfurylidene-3,4-dihydro-1(2*H*)-phenanthrenone (Table 3). By the same token, furfurylidenecyclohexanone, and the related furfurylidenecyclopentanone, would be expected to show a similar behavior, although this has not been reported. On the other hand, failure of an attempt[61] to effect the typical transforma-

[62] Kehrer and Igler, *Ber.*, **34**, 1263 (1901).
[63] Blicke, Warzynski, Faust and Gearien, *J. Am. Chem. Soc.*, **66**, 1675 (1944).
[64] Turner, *J. Am. Chem. Soc.*, **71**, 612 (1949).
[65] Martin and Robinson, *J. Chem. Soc.*, **1943**, 497.
[66] Robinson and Todd, *J. Chem. Soc.*, **1939**, 1747.
[67] Courant and Kostanecki, *Ber.*, **39**, 4031 (1906).
[68] Marini-Bettolo, *Gazz. chim. ital.*, **71**, 635 (1941); *C. A.*, **37**, 123 (1943).
[69] Butenandt, Dannenberg and Dresler, *Z. Naturforsch*, **4b**, 69 (1949); *C. A.*, **44**, 3966 (1950).

tion with difurfurylidenecyclohexanone, XXXII, suggests that, in this instance the opposing effects of the two identical conjugated systems interfered in some way with the cleavage reaction. In this regard, it is unfortunate that no information is available on the behavior of difurfurylideneacetone, XXXIII, in this reaction, inasmuch as its structural configuration is closely related to that of XXXII, except of course, that its ene-one systems are not involved in a ring structure.



XXXII



XXXIII

In summary, it can be said that acid-catalyzed hydrolysis (alcoholysis) of the furan nucleus may proceed in at least two directions depending upon the role played by nuclear substituents. That is, the initial attack by acid may occur at the nucleus (Table 1), or at a substituent group (Tables 2 and 3), and as has been shown, the site of this attack is of considerable consequence with regard to the nature of the cleavage product. However, the evidence now available is incomplete, and it must be said that the two courses may not be mutually exclusive, except of course, in those instances where the substituents, if any, are incapable of coordinating with an acidic reagent.

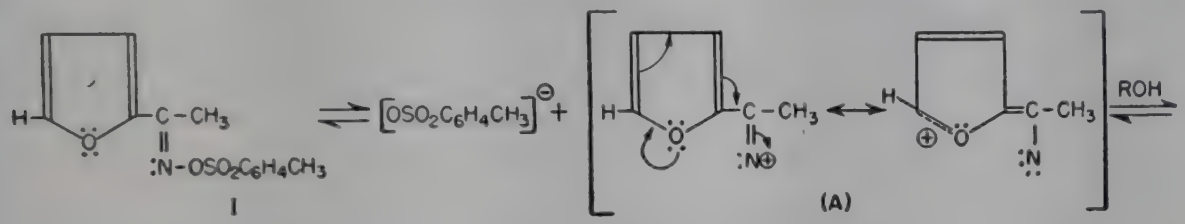
Basic Medium

Furan, and its homologs,° and other types wherein the nucleus is relatively electron-rich are very stable toward aqueous or alcoholic alkali. In view of what has gone before, however, it is not surprising to learn that those furan compounds which exhibit a high degree of acid-stability are, to a greater or lesser extent, subject to nuclear attack, by suitable electron donor reagents. That is, the same electron-withdrawal effect of certain

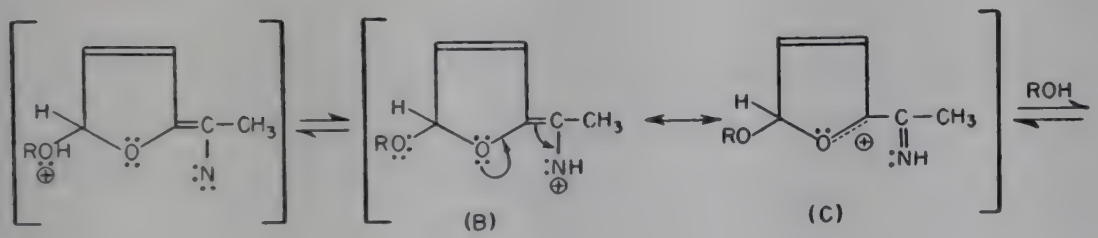
° Conflicting data have appeared in the literature with regard to the effect of alkali on 2-methylfuran (see [70, 1, 71, 72]). However, recent work[28] had demonstrated that pure methylfuran is unaffected when refluxed for 10 hours in 28 per cent aqueous sodium hydroxide. It is believed that, in the earlier work, the methylfuran employed contained impurities, possibly acidic products as a consequence of autoxidation. The latter become highly colored in alkali, and are extracted into the aqueous phase when such impure methylfuran is treated with aqueous alkali. This phenomenon might well account for the earlier reports attributing alkali-instability to methylfuran.

substituents (NO_2, COR, CHO) which was earlier proposed to account for the resistance of these types to acids, may be considered to condition the nucleus for coordination with electron donor reagents. Whether or not such coordination leads to cleavage depends, of course, on the nature of the donor reagent which includes such compounds as sodium hydroxide, miscellaneous nitrogen bases (p. 666), the Grignard reagent and butadiene, among others.

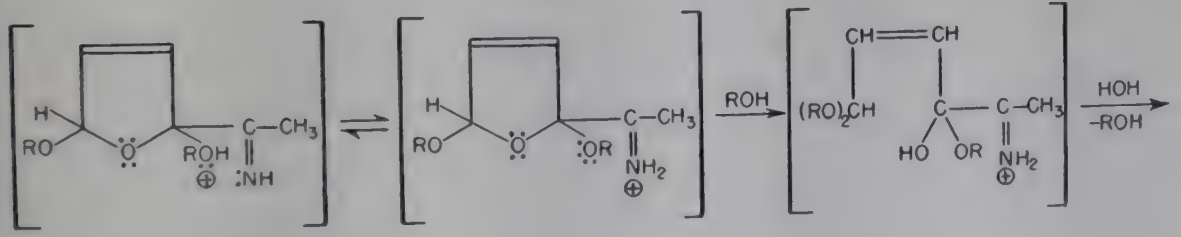
The recently described fission of the tosylated oxime of 2-furyl methyl ketone, I, is seen as an extreme example wherein the 5-position of the furan nucleus is sufficiently electropositive in character to coordinate with even such a weak base as alcohol. When I is shaken with 95 per cent ethanol at room temperature, ammonium *p*-toluenesulfonate is precipitated, and the acetal of 2-hexen-4,5-dione-1-al, II, may be isolated from the mother liquor in 80 per cent yield.[p 73,74] A possible mechanism to account for this extremely



I (A)



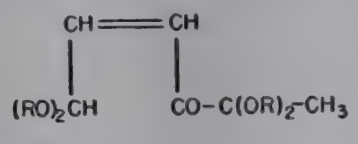
(B) (C)



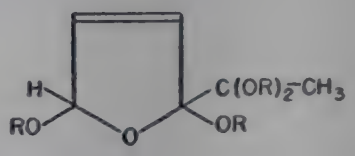
II

[p] Vargha *et al.*[73, 74] had hoped to obtain the *p*-toluenesulfonic salt of 2-aminofuran, but instead observed the result indicated above. In later work, they[75] (see also [76]) demonstrated that the tosylated oximes of several other 2-furyl alkyl ketones behaved similarly; that on the contrary, these same derivatives of 2-furyl aryl ketones undergo the Beckmann rearrangement, producing by subsequent hydrolysis 2-furanilide, and related types. It is clear from the latter result that the 2-furyl aryl

mild transformation is outlined above. The initial step involves ionization of I, followed by coordination of alcohol with the resonating ion, A. Intramolecular oxidation-reduction is involved; the nitrogen is reduced while the nucleus undergoes oxidation. Hydrolysis of all intermediates preceding B would give rise to hydroxylamine, after C, ammonia, the known product of reaction. To obtain II as the other product, it is necessary to assume that a stoichiometric quantity of water is involved in the reaction. Yet Vargha[75] reports II, as the aldoxime derivative, when I is exposed to *absolute* alcohol. Since the latter procedure would have been expected to give rise to D or E, the isolation of the aldoxime of II on subsequent treatment with aqueous hydroxylammonium chloride is not surprising. More difficult to explain is the reported failure of I, in ether, to react with water.[75] Possibly this can be ascribed to limited solubility.

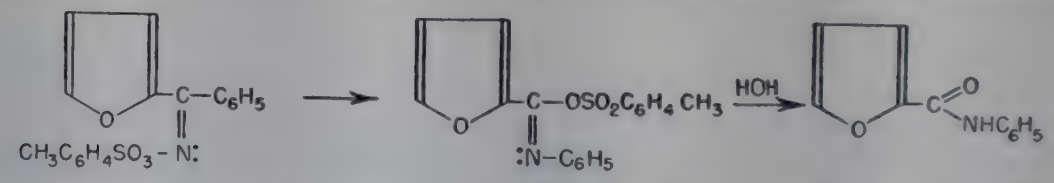


(D)



(E)

Elsewhere (p. 149), the extreme sensitivity of 2-nitrofuran toward aqueous alkali was reported and explained in terms of the susceptibility of the number 5 carbon atom to attack by hydroxyl ion. That a cleavage reaction takes place under these conditions is indicated by the aldehydic nature of the product(s), although it must be admitted that the latter is resinous in character and of obscure composition. More clean-cut evidence for alkaline cleavage is at hand in connection with the behavior of 5-phenyl-3-benzoyl-



ketoximes possessed the *syn*-configuration with reference to the furan ring. The different behavior of the 2-furyl alkyl ketoximes may be due to (1) the reverse (*anti*) configuration, or (2) it may be related to intrinsic migratory aptitude of aryl versus alkyl groups (see [77]). In the text, I has been given the *anti*-configuration although this is not known with certainty.

[70] Atterberg, *Ber.*, **13**, 879 (1880).

[71] Gilman and Breuer, *J. Am. Chem. Soc.*, **56**, 1123 (1934).

[72] Gilman and Wright, *Chem. Revs.*, **11**, 323 (1932).

[73] Vargha, Ramonczai and Bite, *Nature*, **159**, 744 (1947).

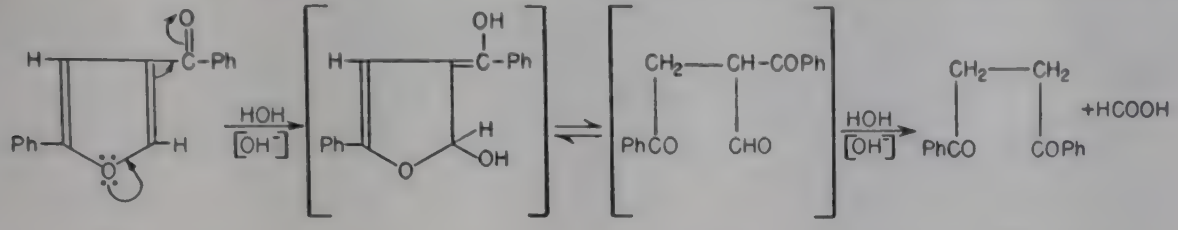
[74] Vargha, Ramonczai and Bite, *J. Am. Chem. Soc.*, **70**, 371 (1948).

[75] Vargha and Gönczy, *J. Am. Chem. Soc.*, **72**, 2738 (1950).

[76] Vargha, Ramonczai and Bathory, *J. Am. Chem. Soc.*, **71**, 2652 (1949).

[77] Wheland, "Advanced Organic Chemistry," 2nd Ed., p. 513, New York, John Wiley and Sons, Inc. (1949).

furan, III, which on treatment with aqueous sodium hydroxide gives rise to 1,2-dibenzoylethane, IV, and formic acid.[78] In this instance, it is the number 2 carbon of the nucleus which is relatively electropositive, and the outcome is attributable to attack by hydroxyl ion[q] at this location and the subsequent steps outlined below. The final step, degradation of the proposed intermediate (F) is in accordance with the well-known behavior of β-dicarbonyl compounds in alkali. It is anticipated that this reaction could be

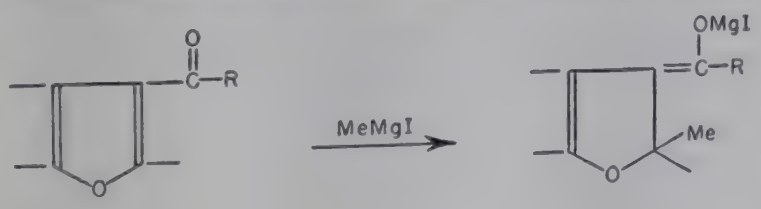


III (F) IV

shown to be quite general to 3-furyl ketones, in the absence of a substituent which would effectively block the entry of an hydroxyl group at the 2-position. In this regard, however, complications are to be expected where the ketones possess the grouping —CO—CH<, since these types would also be subject to the alkali-catalyzed condensation reactions common to this class.

In the same way, 2-furyl ketones are susceptible to attack by electron donor reagents at the 5-position of the nucleus, as has been amply demonstrated when the attacking reagent is ammonia or an amine (p. 667). It is more difficult, however, to demonstrate that hydroxyl ion coordinates in a similar manner. For example, 2-furyl phenyl ketone is slowly attacked by hot, aqueous sodium hydroxide, but the sole product isolated to date is a resinous material of, as yet, undetermined constitution.[28] Accordingly, there is no evidence at this time to support the belief that 2-furyl ketones are

[q] Related is the work of Lutz and Reveley[79] showing that, in at least one instance, the Grignard reagent can react with a 3-acylfuran (V, R = mesityl) in such manner as to produce the 1,4-type addition compound, VI (see also p. 443). That is, the bulky



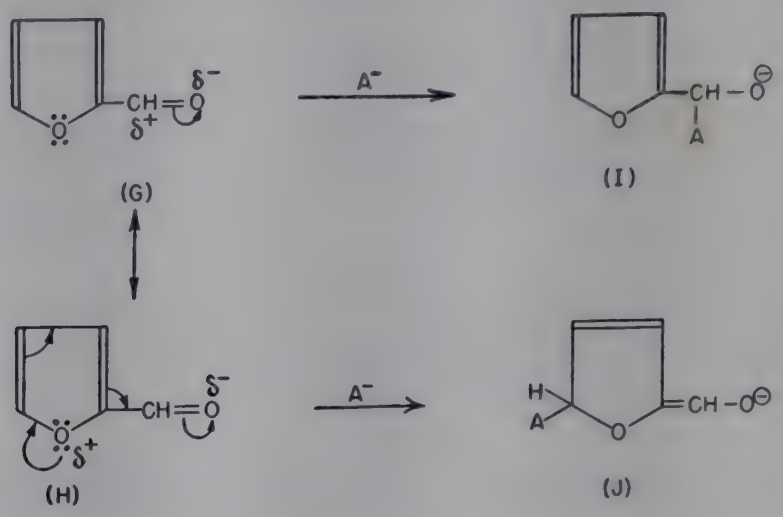
V VI

mesityl group (R) blocks the entrance of the methyl carbanion (from the reagent) at the carbonyl carbon atom where it would normally go in the more common 1,2-type addition reaction.

[78] Fuson, Fleming and Johnson, *J. Am. Chem. Soc.*, **60**, 1994 (1938).

subject to nuclear cleavage by aqueous alkali, although this is a reasonable hypothesis.

With furfural, the situation is similar. That is, consideration of two of the structures, G and H, which contribute to the actual configuration of this aldehyde suggests that in reaction with basic (donor) reagents,[r] one might expect at least two different products, arising by way of intermediates I and J. The most common, and in any case the most predominant, reaction

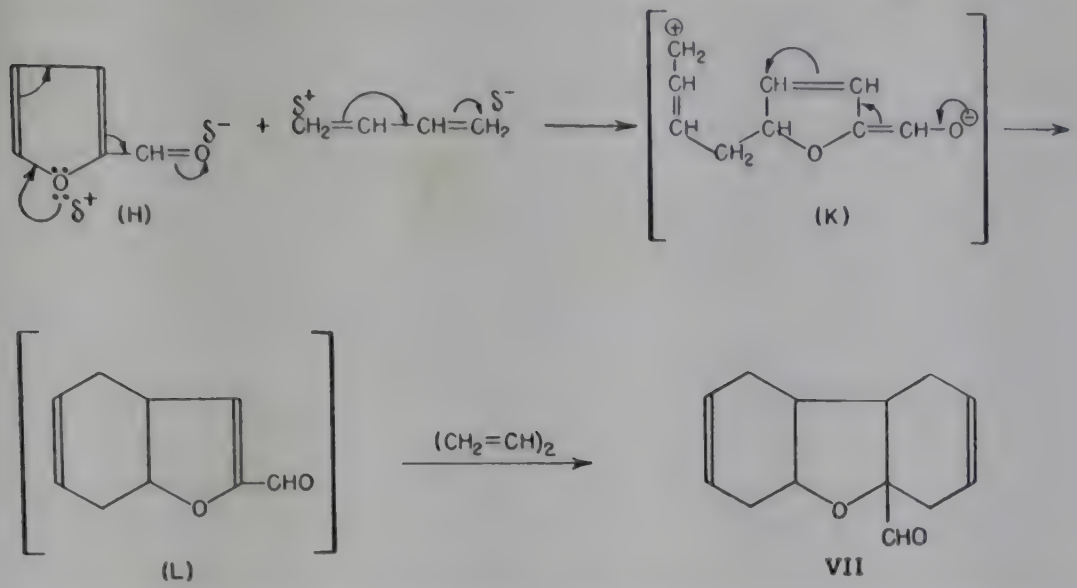


is that wherein furfural behaves in accordance with structure G; 1,2-type addition reactions of the carbonyl group, as in the Cannizzaro reaction, aldol condensations, aldimine formation, and others. In most instances, however, side reactions are observed. Dark colored, resinous by-products are generally obtained together with the expected reaction product(s). While lack of evidence precludes a definite statement attributing the former, even in part, to nuclear attack along the lines indicated by equation (H) → (J), this is not an unlikely explanation. For instance, reaction of furfural with butadiene (a donor reagent) gives rise to 2,3:4,5-bis-2-butenotetrahydrofurfural, VII[80] (see also p. 62), presumptive evidence that furfural can react in accordance with structure H. In this instance, there is no opportunity for cleavage of the ring because of the nature of the coordinating reagent. Instead, the postulated intermediate, K, can by a simple rearrangement of electrons, cyclize to the equimolecular adduct, L (not isolated), which then adds another molecule of butadiene to form VII.

[r] For purposes of illustration, an anion, A^-, has been selected as the reagent. Among others, this might be OH^-, CN^-, etc., but it could also be an electrically neutral donor reagent such as ammonia, an amine, the Grignard reagent, or even butadiene (see text).

[79] Lutz and Reveley, *J. Am. Chem. Soc.*, **63**, 3178, 3180 (1941).

[80] Hillyer, Swadesh, Leslie and Dunlop, *Ind. Eng. Chem.*, **40**, 2216 (1948).



It will be evident that the only clearly demonstrated example of alkaline cleavage of the furan ring is that due to the work of Fuson[78] with 5-phenyl-3-benzoylfuran (p. 661). The belief that other furans possessing electron-withdrawing substituents are, to some degree, subject to similar fission is, at this time, founded on analogy, and on the behavior characteristics of these types with donor reagents other than hydroxyl ion (see, for instance, p. 666). The need for further experimental work is apparent.

Ammonolytic Fission

Vapor Phase

Passage of furan and its homologs with ammonia[s] over alumina at 400–450° gives rise to the corresponding pyrrole compound as indicated by the data listed in Table 4. With primary amines, N-substituted pyrroles are obtained under like conditions. In all experiments, the yield leaves much to be desired and, in general, it appears that the reaction proceeds more smoothly when applied to tetrahydrofurans which, of course, are converted into the appropriate pyrrolidines[84, 83, 86] (see also [87]).

[s] When hydrogen sulfide is employed in place of ammonia, thiophene and its homologs have been obtained in low yield.[81, 82, 83] Under similar conditions, tetrahydrofuran and its homologs give rise to the corresponding thiophanes in very acceptable yield. For example when 2-methyl-, and 2,5-dimethyltetrahydrofuran are passed, with hydrogen sulfide, over alumina at 400°, 2-methyl-, and 2,5-dimethylthiophane, respectively, are formed in 68–69 per cent yield.[84, 83] For related conversions of furan and tetrahydrofuran into selenophene (23 per cent) and selenophane (54 per cent), see Yur'ev.[85]

[81] Yur'ev, *Ber.*, **69**, 440 (1936).

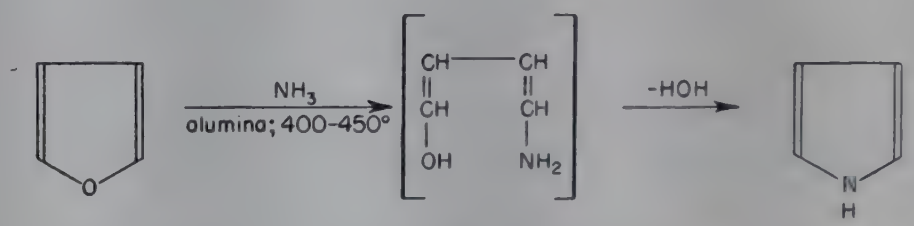
[82] Yur'ev and Tronova, *J. Gen. Chem. U. S. S. R.*, **10**, 31 (1940); *C. A.*, **34**, 4733 (1940).

[83] Yur'ev, Tronova, L'vova and Bukshpan, *J. Gen. Chem. U. S. S. R.*, **11**, 1128 (1941); *C. A.*, **37**, 4071 (1943).

[84] Yur'ev, *J. Gen. Chem. U. S. S. R.*, **8**, 1934 (1938); *C. A.*, **33**, 5845 (1939).

[85] Yur'ev, *J. Gen. Chem. U. S. S. R.*, **16**, 851 (1946); *C. A.*, **41**, 1654 (1947).

Conversion of furan into pyrrole was probably first observed by Schwanert[88], again some years later, by Canzoneri and Oliveri.[89] The latter investigators reported its formation in an experiment in which furoic acid was heated (280°) with ammonia and zinc chloride, and postulated decarboxylation of the acid to furan which then reacted with the ammonia. The reaction was more or less neglected until recent years when Yur'ev and his associates[81, 90, 91, 92, 93] embarked on an extensive study involving the application of vapor phase techniques. They[92] (see also [87]) propose that the conversion proceeds by way of aminative cleavage of furan to 4-amino-1,3-butadien-1-ol, followed by dehydration to pyrrole. Concerning the other products of reaction, they report carbon monoxide and unidentified hydrocarbons, but reëxamination of the reaction by Wilson[95] has revealed the presence of indole, carbazole and pyrrocoline in the product mixture. These are considered to arise by reaction of pyrrole with itself, since the yield of pyrrole appears to be independent of the concentration of unreacted furan.[95]



Furfuryl alcohol fails to react with ammonia under similar conditions, but tetrahydrofurfuryl alcohol is attacked with formation of pyridine (3 per cent) and piperidine (9 per cent)[96] (see also [97]), and it has been reported [87, 98] that the yield of the former can be increased to 67–70 per cent, under optimum conditions, over chromia-alumina or phosphate catalysts. Pyridine is also obtainable, together with a greater quantity of N-tetrahydrofurfurylpiperidine, by catalytic hydrogenation of furfurylamine in the liquid phase.[99] In all likelihood this reaction proceeds by way of tetrahydrofurfurylamine,

[86] Yur'ev, Aleksandrov, Arbatskii, Karataev, Korobitsyna, and Pryanishnikova, *Zhur. Obschei Khim. J. Gen. Chem.*, **19**, 1730 (1949); *C. A.*, **44**, 1482 (1950).

[87] Natta, Mattei and Bartoletti, *Chimica e industria*, **24**, 81 (1942); *C. A.*, **37**, 6261 (1943).

[88] Schwanert, *Ann.*, **116**, 257 (1860).

[89] Canzoneri and Oliveri, *Gazz. chim. ital.*, **16**, 476 (1886).

[90] Yur'ev, *Ber.*, **69**, 1002 (1936).

[91] Yur'ev, *Ber.*, **69**, 1944 (1936).

[92] Yur'ev and Rakitin, *Ber.*, **69**, 2492 (1936).

[93] Yur'ev, *J. Gen. Chem. U. S. S. R.*, **8**, 116 (1937); *C. A.*, **32**, 5399 (1938).

[95] Wilson, *J. Chem. Soc.*, **1945**, 63.

[96] Kline and Turkevich, *J. Am. Chem. Soc.*, **66**, 1710 (1944).

[97] Mattei, *Ricerca sci.*, **13**, 783 (1942); *C. A.*, **39**, 2024 (1945).

[98] Natta, Mattei and Bartoletti, Italian Pat. 382,819 (1940); *Chem. Centr.*, **1942**, **I**, 2930.

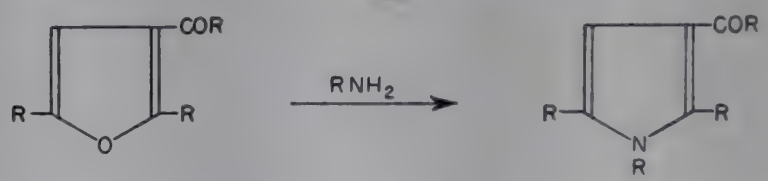
[99] Wilson, *J. Am. Chem. Soc.*, **67**, 693 (1945).

Reactants	Temp. (°C.)	Catalyst	Product	Yield (%)	Ref.
Furan + NH_3	400	alumina	pyrrole	19	95
+ NH_3	450	alumina	pyrrole	30	81; see also 101
+ NH_3	550	alumina	pyrrole	40	92
+ NH_3	450	thoria	pyrrole	16	92
+ NH_3	370–480	MoO_3, or V_2O_5 on alumina	pyrrole	—	102
+ CH_3NH_2	400–440	alumina	1-methylpyrrole	24	84
+ $C_2H_5NH_2$	400–440	alumina	1-ethylpyrrole	27	84
+ $C_5H_{11}NH_2$	465–470	alumina	1-pentylpyrrole	14	86
+ $C_6H_5CH_2NH_2$	460	alumina	1-benzylpyrrole	3	83
+ $C_6H_5NH_2$	465	alumina	1-phenylpyrrole	24	91
+ *o*-$CH_3C_6H_4NH_2$	465	alumina	1-*o*-tolylpyrrole	41	91
+ *p*-$CH_3C_6H_4NH_2$	465	alumina	1-*p*-tolylpyrrole	21	91
2-Methylfuran + NH_3	450	alumina	2-methylpyrrole	24	90
+ NH_3	—	chromia-alumina	2-methylpyrrole	—	87
+ $C_6H_5NH_2$	475	alumina	1-phenyl-2-methylpyrrole	12	93
+ *o*-$CH_3C_6H_4NH_2$	475	alumina	1-*o*-tolyl-2-methylpyrrole	10	93
+ *p*-$CH_3C_6H_4NH_2$	475	alumina	1-*p*-tolyl-2-methylpyrrole	10	93
2-Ethylfuran + NH_3	450	alumina	2-ethylpyrrole	5	86
2,5-Dimethylfuran + NH_3	350–450	alumina	2,5-dimethylpyrrole	16	83

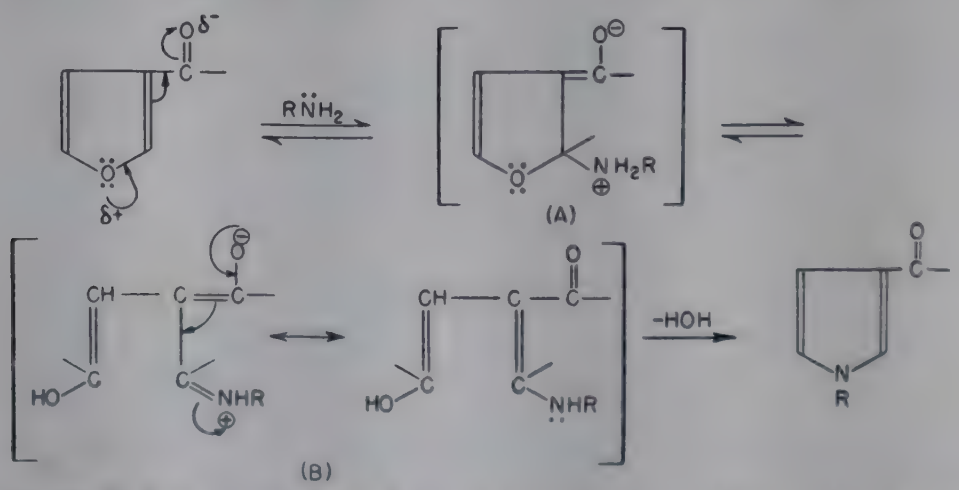
and is, presumably, related to the patented procedure of Schmidt *et al.*,[100] who report the preparation of pyridine and piperidine by reductive amination of furfural or its hydrogenated derivatives.

Liquid Phase

While rather strenuous temperatures are required for aminative cleavage of furan and its homologs, similar fission of furans with electron-withdrawing substituents can be achieved under considerably milder conditions. Such a reaction was first observed before the turn of the century, when Magnanini and Bentivoglio[103] reported the formation of 2,5-dimethyl-3-acetylpyrrole when the analogous furyl ketone was heated with ammonia at 110–115°. Forty years later, Fuson[78] showed that 5-phenyl-3-furyl phenyl ketone was subject to similar cleavage, and described its transformation into 5-phenyl-3-benzoylpyrrole by the action of ammonia in aqueous-alcoholic medium; into 1,5-diphenyl-3-benzoylpyrrole on refluxing with

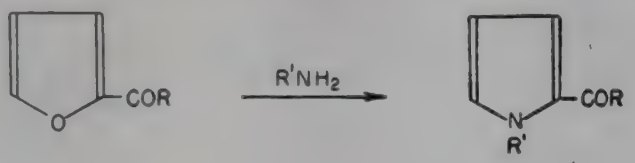


aniline. These conversions are related to the alkaline-catalyzed hydrolytic fission of such furan types, and are subject to similar explanation, except that in this instance, the nature of the intermediate cleavage product, B, is such as to permit recyclization, with loss of water, to form a new heterocycle. That is, initiation of reaction can be formulated as an attack by the donor reagent (ammonia or amine) at the relatively electropositive 2-carbon atom of the furan nucleus, giving rise to A as illustrated below (compare attack by hydroxyl ion, p. 661.



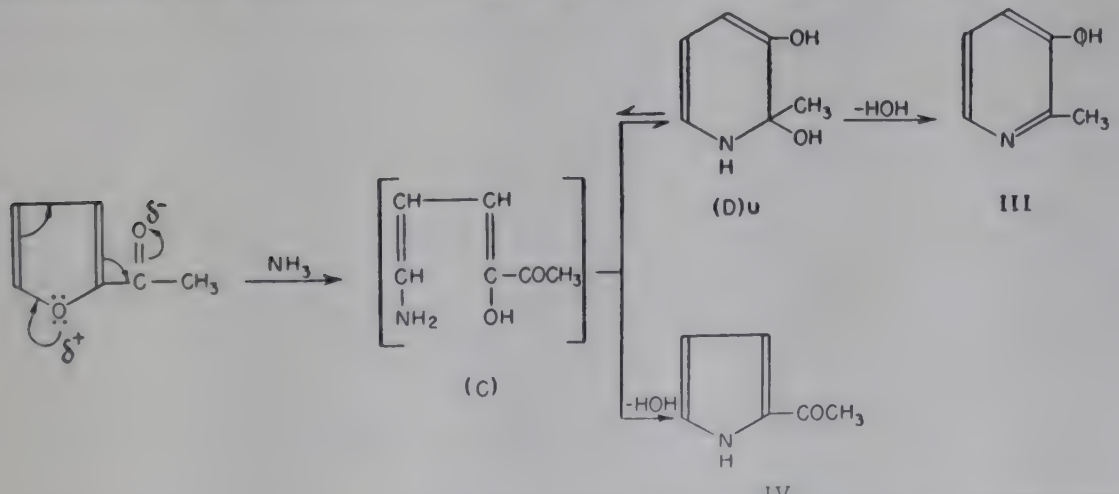
Recently[28] it has been found that similar transformations occur with 2-furyl ketones, indicating by analogy with the scheme presented above that the nuclear 5-carbon atom of these types is relatively electron-poor,

and able to accept an electron pair donated by nitrogen bases. Thus, when 2-furyl methyl ketone, I (R = CH_3) is heated at about 150° with *n*-butylamine, one obtains 1-*n*-butyl-2-acetylpyrrole, II (R = CH_3; R′ = *n*-C_4H_9). By appropriate selection of I (R = CH_3, C_2H_5, C_6H_5), and of the attacking amine (R′ = *n*-C_4H_9, dodecyl), it has been possible to prepare quite a variety of substituted pyrroles. Accordingly, the reaction appears to be of more or less general application. It goes forward quite readily in aqueous or aqueous-alcoholic medium or in an excess of the amine itself, but fails to occur, at least at any reasonable rate, in ether. Additionally, it has been observed that 5-methyl-2-acetylfuran is more slowly attacked than 2-furyl methyl ketone, a result which might be attributed to steric influences, but perhaps more so to the electron-field effect of the methyl radical acting to decrease the electropositive character of the nuclear 5-carbon atom. From the standpoint of steric hindrance, it would be interesting to attempt the reaction with 5-*t*-butyl-2-acetylfuran. The use of ammonia in place of an



I II

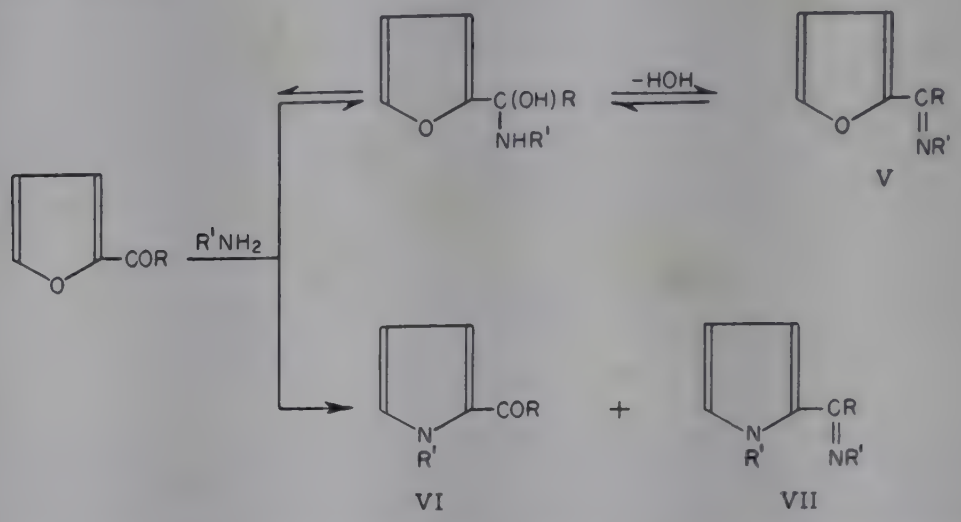
amine introduces some complexities since, in this instance, the intermediate (C) can cyclize in two different directions, one leading to a pyrrole, and the other to a β-pyridol.[t] Aqueous medium favors the latter reaction, such that 2-furyl methyl ketone and ammonium hydroxide gives rise to 2-methyl-3-pyridol, III, in 47 per cent yield, with very little, if any, 2-acetylpyrrole, IV. On the other hand, the same reaction using alcoholic ammonia produced a mixture of III (10 per cent) and IV (38 per cent).[28] Competitive with



[t] The related intermediate (B; R = H) derived from ammonia and a 3-furyl ketone cannot cyclize to a 6-membered nitrogen heterocycle.

[u] While a similar dihydropyridine intermediate is possible when a primary amine

these nuclear transformation reactions is the formation of the appropriate furyl ketimine, V (1,2-type addition of an amine to the carbonyl group). To the extent that this reaction occurs, the yield of the new heterocycle (VI and VII) is diminished, presumably because the ketimine group is much less effective than the original carbonyl group in creating an electropositive center in the furan nucleus. Thus, it has been found that V (R = CH_3; R′ = n-C_4H_9) fails to produce a pyrrole compound when treated with n-butylamine, whereas 2-furyl methyl ketone under similar conditions, gives a mixture of V, VI and VII.[28] The reactions involves are summarized below:



This may explain, in part at least, the failure to detect similar conversions starting with furfural. That is, the very active carbonyl group of the aldehyde appears to react almost exclusively to give the corresponding aldimine which, like the related ketimine (V) is not particularly susceptible to nuclear attack by basic reagents. Of course the difficulty here may also be attributable to ease of resinification of the various possible products and intermediates. Certainly, much resin is produced when furfural is subjected to the action of amines, or ammonia at elevated temperature; at room temperature, aldimines or hydrofuramide (or furfurin), respectively, are

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is used in place of ammonia, conversion of such to III would require elimination of the elements of the appropriate alcohol (ROH). While the latter might be accomplished at very high temperatures, there is no evidence that it occurs under the conditions (*ca.* 150°) employed in these experiments. That is, no pyridols have been obtained, to date, from the reaction of 2-furyl ketones with primary amines. N-substituted-2-pyrryl ketones, as such or in the form of the appropriate ketimine, are the only heterocyclic products which have been isolated.[28]

[100] Schmidt, Blaser and Manchen (to I. G. Farbenindustrie Akt.-Ges.) German Pat. 695,472 (1940); *C. A.*, **35**, 5520 (1941).

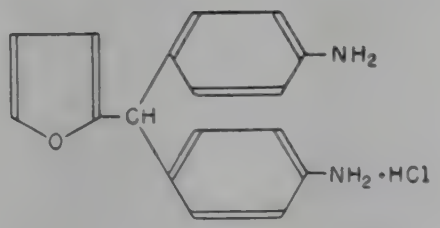
[101] Keil and Dobke (to Temmler-Werke, Vereinigte chemische Fabriken Hermann Temmler), German Pat. 706,095 (1941); *C. A.*, **36**, 1957 (1942).

[102] Bishop and Denton (to Socony-Vacuum Oil Co.) U. S. Pat. 2,478,452 (1949); *C. A.*, **44**, 665 (1950).

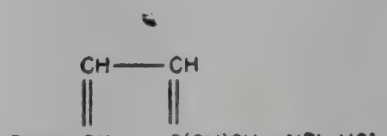
[103] Magnanini and Bentivoglio, *Gazz. chim. ital.*, **24, I**, 433 (1894).

formed in high yield. Accordingly, little can be said at this time with regard to ammonolytic cleavage as it may apply to furfural; that is, cleavage under the conditions which have been shown to be effective with the acylfurans.

Related to this subject, however, is the fission of furfural by the action of primary, aromatic amine salts. Thus, it has been known for many years that treatment of the aldehyde with these amines in acidic medium gives rise to highly colored compounds,[v] frequently referred to in the literature as "Stenhouse dyes" in recognition of their discoverer[104, 105] (see also [106]). For example, when equimolecular quantities of furfural, aniline, and aniline hydrochloride are mixed in alcoholic solution, a purple, crystalline mass is deposited, the constitution of which has been the subject of some controversy. By analogy with the formation of triphenylmethane dyes, Schiff[107, 108] (see also [109]) assigned structure VIII. However, the evidence[110, 111, 112] (see also [113]) favors that of β-hydroxyglutaconaldobisphenylimine hydrochloride (IX), the case for which has been admirably presented by Williams and Wilson.[114] The following additional references should be consulted for additional information and for application of the reaction to other aromatic



VIII



IX

amines.[115, 116, 117, 118, 119] The presence of hydrogen chloride (or other acid) is a necessary condition. No similar reaction occurs with aniline alone, which gives rise to the aldimine, X. A possible explanation is that X is

[v] This reaction is the basis of well-known colorimetric procedures for the determination of furfural (p. 308).

[104] Stenhouse, *Ann.*, **74**, 278 (1850).

[105] Stenhouse, *Ann.*, **156**, 197 (1870).

[106] Persoz, Wagner's Jahresberichte der Technologie für 1860, p. 487; *Chem. Centr.*, **1862**, 10.

[107] Schiff, *Ann.*, **201**, 355 (1880).

[108] Schiff, *Ann.*, **239**, 349 (1887).

[109] Riegel and Hathaway, *J. Am. Chem. Soc.*, **63**, 1835 (1941).

[110] Zincke and Mühlhausen, *Ber.*, **38**, 3824 (1905).

[111] Dieckmann and Beck, *Ber.*, **38**, 4123 (1905).

[112] König, *J. prakt. Chem.*, **72**, 555 (1905).

[113] Aschan and Schwalbe, *Ber.*, **67**, 1830 (1934).

[114] Williams and Wilson, *J. Chem. Soc.*, **1942**, 506.

[115] Fischer, Balling and Aldinger, *J. prakt. Chem.*, **100**, 86 (1919).

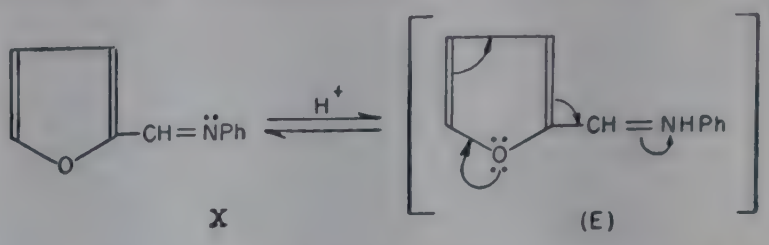
[116] Boehm, *Arch. Pharm.*, **267**, 129 (1929); *Chem. Centr.*, **1929, I**, 2183.

[117] König, Hey, Schulze, Silberkweit and Trautmann, *Ber.*, **67**, 1274 (1934).

[118] Boehm and Grohnwald, *Arch. Pharm.*, **274**, 318 (1936).

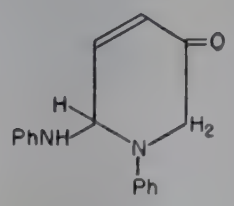
[119] Loewenstein, Thesis, Friedrich-Wilhelms University, Berlin, 1931.

formed as an intermediate, and subsequently coordinates with a proton to produce the resonating ion E, which may then be attacked by aniline at the 5-carbon atom of the furan nucleus, in the manner discussed previously.

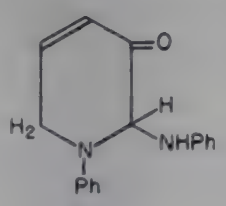


X (E)

Early attempts to form the free base corresponding to IX resulted in the formation of amorphous solids, or resins.[104, 105, 107, 108, 110] More recently, however, McGowan[120] succeeded in obtaining such a base in crystalline form (23 per cent yield), and on the basis of its properties, concluded that it possessed a cyclic structure, either XI or XII. The existence of the salt, IX, in the open, enolic form is attributable to the stabilization of this



XI



XII

structure by resonance (see diagram below); an effect which would be weakened considerably by formation of the free base. The scheme illustrated below predicts two isomeric forms of the latter (XI A and XII A; shown in enolic form[w]), yet only one specie has been obtained,[120] even in later work[28] in which the yield has been increased to 50 per cent. An explanation is not immediately apparent. Also illustrated, is the conversion of IX to 1-phenyl-3-hydroxypyridinium chloride, XIII, a thermal degradation which proceeds with elimination of the elements of aniline. Compounds related to IX and/or XIII have been prepared in a similar manner from 5-halofurfurals,[121] from furylacrolein,[122] and from 2-furyl ketones.[123] For the formation of "Stenhouse dyes" from furfural and *o*-, *m*- and *p*-aminobenzenearsonic acids, see Kuznetsov and Vasyunia[124]; from furfural and sulfanilamide, see Vignoli and Sicé.[125] No similar reaction has yet been

[w] By appropriate prototropic rearrangements, the relationship of XI A and XII A to XI and XII, respectively, will be apparent.

[120] McGowan, *J. Chem. Soc.*, **1949**, 777.

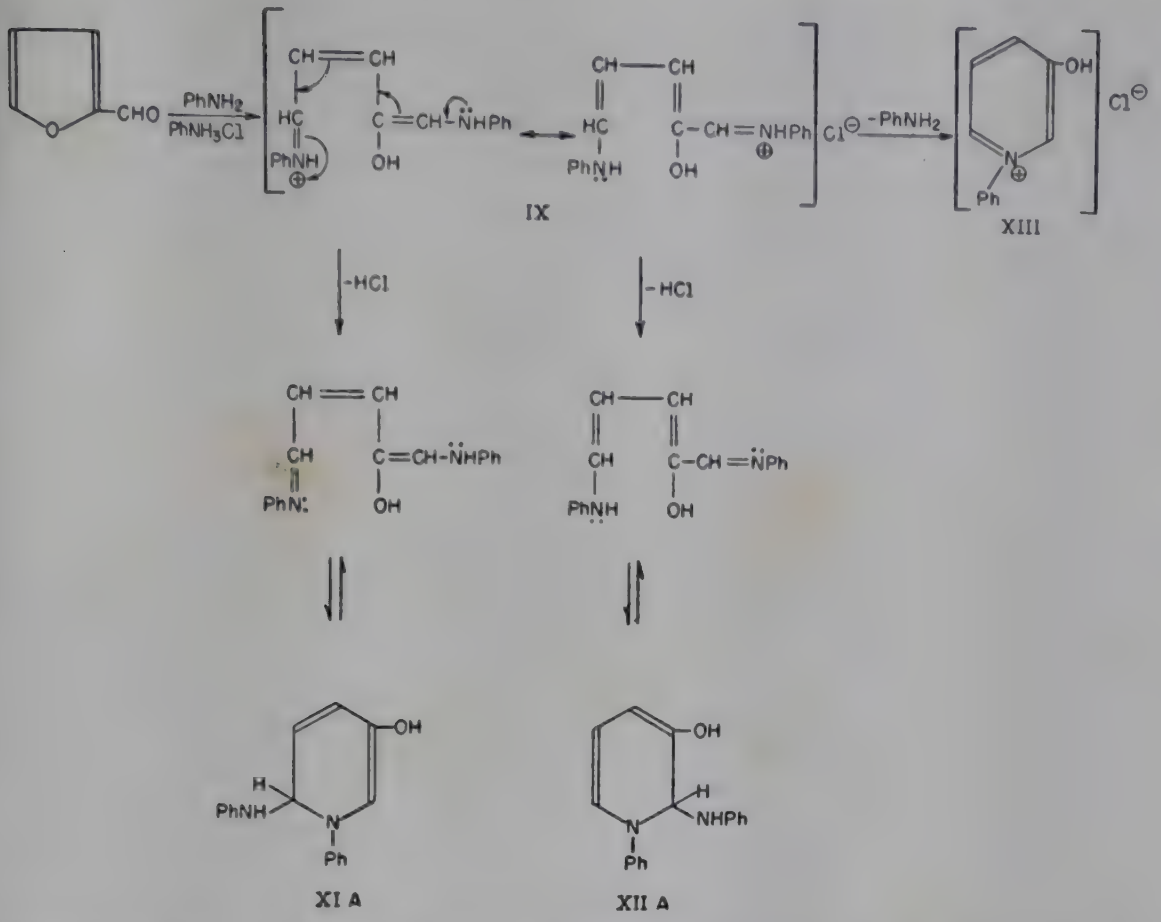
[121] Hewlett, *Iowa State Coll. J. Sci.*, **6**, 439 (1932).

[122] König, *J. prakt. Chem.*, **88**, 193 (1913).

[123] Borsche, Leditschke and Lange, *Ber.*, **71**, 957 (1938).

[124] Kuznetsov and Vasyunina, *J. Gen. Chem. U. S. S. R.*, **10**, 1203 (1940); *C. A.*, **35**, 2868 (1941).

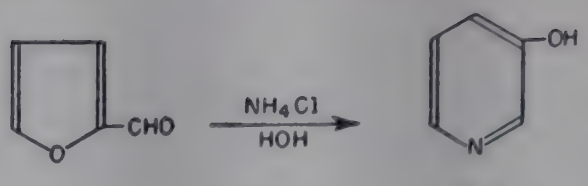
[125] Vignoli and Sicé, *Bull. soc. chim.*, **12**, 877 (1945).



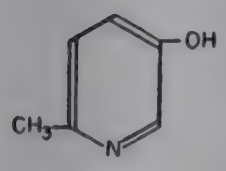
described using aliphatic amines, possibly because these stronger bases completely tie up the added acid and thus, nullify its function in creating an electropositive center in the furan ring as postulated above.

Under certain conditions, a cleavage reaction also takes place when aqueous ammonium salts are used in place of the aromatic amine salt. This is indicated by the work of Aso[126, 127] who made a rather extensive study of the action of ammonium chloride, sulfate and oxalate among others, on aqueous solutions of several furan aldehydes. While the reaction responsible for cleavage is probably hydrolytic rather than ammonolytic in nature, it is appropriate to discuss it at this point because of the character of the isolated products. Elevated temperatures (*ca.* 150–160°) were employed, promoting thereby, not only resinification, but also recyclization of intermediate, open-chain types to pyridols, which were isolated in rather low yield (2–10 per cent). In this manner, furfural gave rise to 3-pyridol, XIV; the homolog, XV, was derived from 5-methylfurfural. From either 5-(chloromethyl)- or 5-(ethoxymethyl)furfural, two products were obtained: 6-(hydroxymethyl)-3-pyridol, XVI, and the isomeric 6-methyl-2,3-pyridinediol, XVII, the latter presumably by rearrangement of XVI. Aso[126, 127] also investigated the action of hot, aqueous hydroxylam-

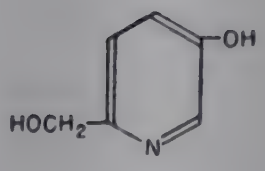
[126] Aso, *Bull. Inst. Phys. Chem. Res. Tokyo*, **18**, 171, 177, 182 (1939).
[127] Aso, *J. Agr. Chem. Soc. Japan*, **16**, 249, 253 (1940).



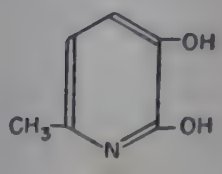
XIV



XV

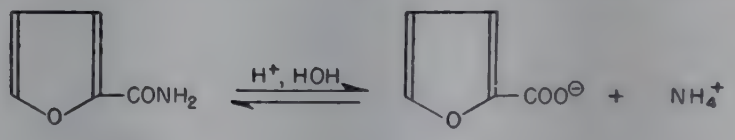


XVI



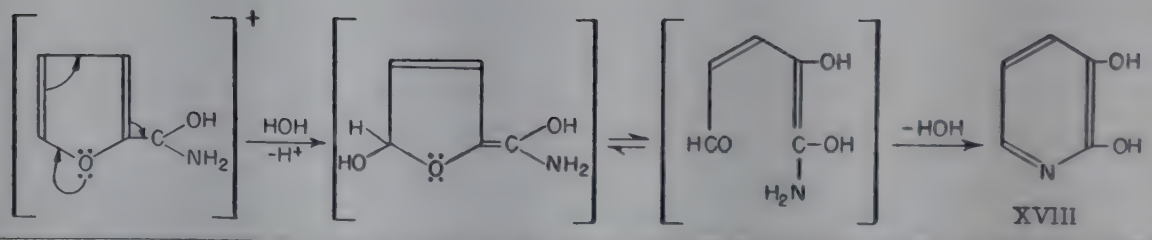
XVII

monium salts on furfural, and on 5-methylfurfural, and succeeded in isolating 2,3-pyridinediol,[x] XVIII, and its 6-methyl homolog, XVII, respectively. He postulated that the first-formed aldoximes underwent rearrangement to the corresponding amides (2-furamide, XIX, in the case of furfural); that the latter were cleaved and then recyclized to the appropriate pyridols. This seems reasonable, especially in view of the fact that furoic acid was also formed among the products of the reaction with furfural. By way of confirmation, Aso showed that XVIII could be obtained in low yield from XIX by heating the latter at 150–155° for several hours in aqueous hydrochloric acid. In accordance with the concepts discussed previously, this



XIX





XVIII

[x] Aso[126, 127] originally assigned the 2,5-dihydroxy structure to XVIII, since he showed his product to be identical with that described earlier by Kudernatsch[128] as 2,5-pyridinediol. Proof that the latter was actually the 2,3-isomer was presented by Schickh, Binz and Schulz[129] in 1936, but apparently this paper was not available to Aso at the time of his initial reports. In his later reports, Aso revised his structures accordingly.

[128] Kudernatsch, *Monatsh.*, **18**, 613 (1897).

[129] Schickh, Binz and Schulz, *Ber.*, **69**, 2593 (1936).

conversion can be formulated as outlined below. Treatment of furfural with hydrazine sulfate under similar conditions produced both XIV and XVIII. Aso explained this result on the basis that the reagent undergoes hydrolysis to ammonia and hydroxylamine, which then react separately in accordance with the discussion presented above.

Chapter 15

CATALYTIC HYDROGENATION OF FURANS

(*Contributed by* SAMUEL SWADESH*)

Reduction, with the exception of catalytic hydrogenation, of furan compounds has been treated, in general, as part of the reactions of the particular furan in question. It was felt that because of the often unpredictable qualities inherent in heterogeneous catalytic processes, catalytic hydrogenation of furans should be treated separately. The reviews on this subject which have been published to date[1, 2, 3] are limited in scope. An attempt has been made here to correlate all of the available information on the behavior of furan compounds with hydrogen under the influence of catalysts. This includes not only addition of hydrogen to unsaturated linkages (hydrogenation) but also fission reactions induced by hydrogen (hydrogenolysis).

THE HYDROGENATION REACTION

Catalysts

No small part in the rate, extent and direction of hydrogenation is played by the catalyst. Generalizations about catalysts should not be taken very seriously. Comparisons cannot be made without taking into account many factors other than catalyst. The method of preparation in a particular laboratory or even of a particular batch may greatly influence the activity of the catalyst. Such variables have been discussed for nickel-on-kieselguhr (Ni(K)), Raney nickel (Ni(R)) and copper-chromite (Cu-CrO) by Adkins.[3] As an extreme example, Raney nickel has been prepared in a way (Adkins' W-7) such that its activity at room temperature compares favorably with that of platinum. In addition, the quantity of catalyst employed, impurities (either deliberately or inadvertently added), time, temperature, pressure, efficiency of shaking, size of batch, solvent, acidity, etc., may, and often do, influence the reaction. In other words, all of the factors which affect a heterogenous catalytic reaction may be operative and the reader should not expect to exactly reproduce any procedure reported in the literature.

* Present address, 7 Millside Lane, Mill Valley, Calif.

[1] Paul, *Bull. soc. chim. France*, **1947**, 158.

[2] Wojcik, *Ind. Eng. Chem.*, **40**, 210 (1948).

[3] Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-chromium Oxide and Nickel Catalysts," Madison, The University of Wisconsin Press (1937).

For purposes of simplification, nickel catalysts will usually be referred to as such, regardless of how prepared, the carrier, other metals added as promoters, etc. As an exception, Raney nickel will be referred to by name because of the marked difference in activity of this catalyst in comparison to the other nickel catalysts reported. Similarly, all copper catalysts are referred to as such, with the exception of copper-chromite which fills a role in the copper group of catalysts, comparable to that of Raney nickel in the nickel group. Platinum and palladium catalysts are also listed, in general, without notation of carrier, mode of preparation, etc. It is felt that the above simplification is justified because usually, while variation in method of preparation of catalyst may affect the rate and sometimes the yield of products, the essential character of the reaction is unaffected.

Particularly important is the distinction of selective hydrogenation made possible by choice of catalyst, or other variable, and that made possible by stopping a stepwise reaction when a particular amount of hydrogen has reacted. This can be illustrated by the hydrogenation of furfural. Over copper-chromite, the hydrogenation will proceed to reduction of the aldehyde to furfuryl alcohol and then stop. Over nickel, three moles of hydrogen will react to give tetrahydrofurfuryl alcohol, but if the reaction is stopped when only one mole of hydrogen has been absorbed, the product will be found to be mainly furfuryl alcohol. The generalizations about catalysts which follow should be taken in light of the above remarks.

Hydrogenation of the furan ring is effected by nickel (usually above 125°), ruthenium, palladium, osmium and platinum catalysts. Platinum may cause serious hydrogenolysis; up to 100 per cent when acetic acid is used as the solvent. Platinum is poisoned by zinc salts so that the furan ring, or an ethylene bond, will be unaffected during hydrogenation.[4] Nickel may be poisoned by chloroform,[5] other halogen compounds and by sulfur. Promotion of nickel catalysts by cobalt, chromium, molybdenum or the platinum group metals has been claimed.[6, 7] However, the most active nickel catalyst is Raney nickel.

Copper catalysts do not cause hydrogenation of the furan ring below about 200°. At higher temperatures, the ring may be attacked but the major reaction is hydrogenolysis. Hydrogenolysis of side groups is encouraged by acidic, and retarded by alkaline conditions. Copper catalysts are markedly promoted by chromite[8] and by compounds of alkali and alkaline earth metals.[9, 10, 11, 12]

[4] Bray and Adams, *J. Am. Chem Soc.*, **49**, 2101 (1927).
[5] Cornubert and Phélisse, *Compt. rend.*, **227**, 1131 (1948).
[6] Paul, *Bull. soc. chim. France*, **1946**, 208.
[7] Delepine and Horeau, *Compt. rend.*, **202**, 995 (1936).
[8] Adkins and Connor, *J. Am. Chem. Soc.*, **53**, 1091 (1931).
[9] Wilson, *J. Am. Chem. Soc.*, **70**, 1313 (1948).

Platinum does not readily give rise to hydrogenation of aldehydes unless a trace of ferrous salt is present as promoter.[4]

Several comparisons have been made of a number of copper and nickel catalysts on the hydrogenation of furfural[13, 14, 15] and on the hydrogenation of furfuryl alcohol.[16]

Solvents

The medium may play an important role in the hydrogenation. For example, Kaufmann and Adams[17] observed no reaction when furfural alone or with 5 per cent water was treated with hydrogen over platinum, but satisfactory reaction was obtained if two volumes of ethanol were employed as a solvent. A comparison of the yield of 3-(2-tetrahydrofuryl)-1-propanol from hydrogenation of 3-(2-furyl)acrolein over nickel[18] showed:

no solvent	15%
1 part ethanol	75%
2 parts ethanol	92%

These marked effects should be borne in mind when referring to the tables in this chapter. The literature is not consistent in reporting the kind and/or amount of solvent used, and in general for this reason, data on solvents have not been included in the tables. The solvent may not only effect the rate but the extent and kind of side reactions. For instance, when platinum was used to catalyze the hydrogenation of furfurylideneacetone to furfurylacetone in three different solvents, Adkins observed the following results[19]:

	yield	
ethanol	36.1%	(encouraged resinification)
ethyl acetate	25.7%	(encouraged addition of more than one mole of hydrogen)
petroleum ether	48.6%	(best of the three solvents)

Competitive Reactions

Hydrogenolysis. Catalytic hydrogenation of the furan ring (I) to the expected tetrahydrofuran compound (II) is complicated in a number of

[10] Lefrancois, *Iowa State Coll. J. Sci.*, **19**, 41 (1944).

[11] Stewart (to Iowa State College Research Foundation), U. S. Pat. 2,400,959 (1946); *C. A.*, **40**, 4860 (1946).

[12] Stanerson, *Iowa State Coll. J. Sci.*, **15**, 104 (1940).

[13] Mizuguchi and Iwase, *J. Soc. Chem. Ind. Japan*, **46**, 1037 (1943); *C. A.*, **42**, 6353 (1948).

[14] Menzel, *Iowa State Coll. J. Sci.*, **12**, 142 (1937).

[15] Bremner and Keeys, *J. Chem. Soc.*, **1947**, 1068; **1949**, 1663.

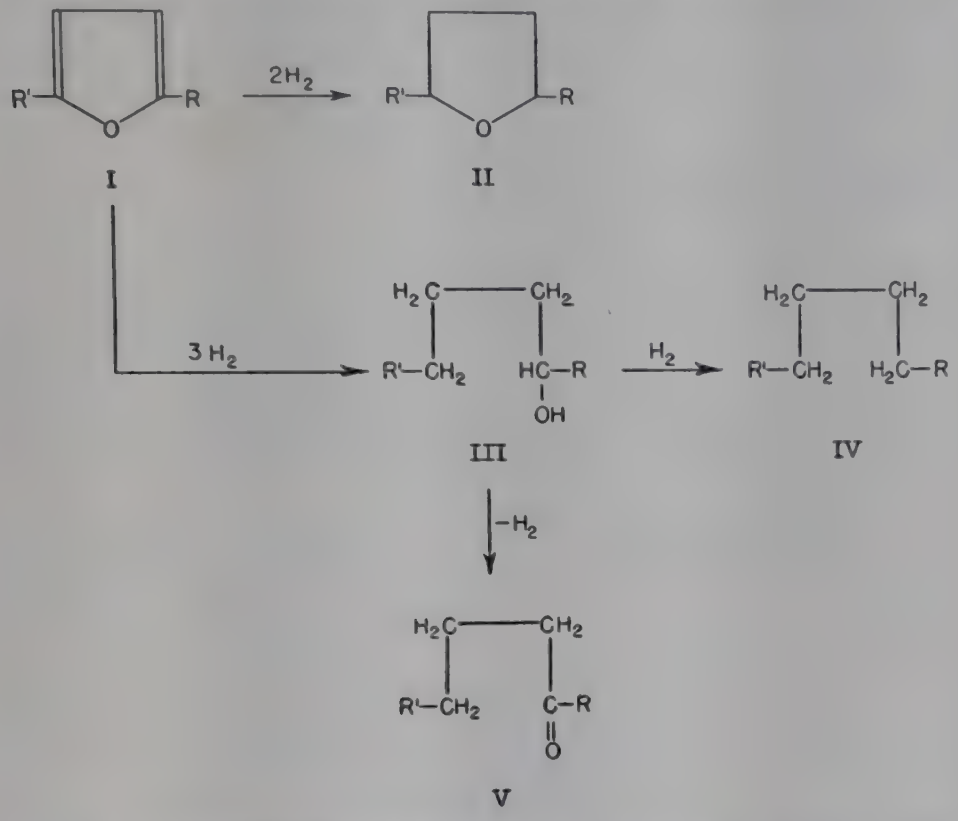
[16] Mizuguchi, *J. Soc. Chem. Ind. Japan*, **46**, 1040 (1943); *C. A.*, **42**, 6802 (1948).

[17] Kaufmann and Adams, *J. Am. Chem. Soc.*, **45**, 3029 (1923).

[18] Hinz, Meyer and Schücking, *Ber.*, **76**, 676 (1943).

[19] Adkins, Diwoky and Broderick, *J. Am. Chem. Soc.*, **51**, 3418 (1929).

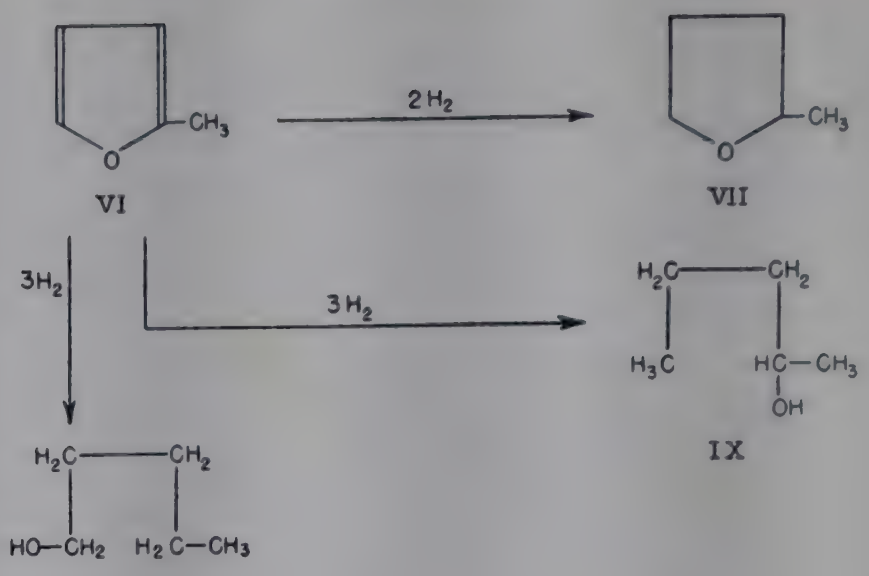
ways. For one thing, hydrogenolysis often occurs simultaneously[20] and even exclusively.[21] It has been demonstrated adequately that hydrogenolysis products III and IV do not arise from II[17, 22] under the experimental conditions employed, but by competitive attack on I. Bradley has measured the rate of hydrogen uptake for the reaction I → III and concluded that three moles of hydrogen react smoothly with no indication of stepwise addition.[23] Further hydrogenolysis may convert the alcohol (III) into the



alkane (IV)[24]; dehydrogenation may give rise to the ketone (V).[25]

The direction of the hydrogenolysis may be influenced greatly by substituents. This is not apparent when R and R′ in I are equal. Furan gives 1-butanol[20], while 2,5-dimethylfuran yields 2-hexanol.[20] When R and R′ are not equal, however, as in 2-methylfuran (VI), both the primary (VIII) and secondary (IX) alcohols might be expected, but only the secondary alcohol is found.[21] In this experiment, therefore, fission occurred exclusively at the 1,5-nuclear C—O bond. Formation of VIII would have required rupture of the corresponding 1,2-bond.

[20] Bremner (to Imperial Chemical Industries Ltd.), British Pat. 586,222 (1947); *C. A.*, **41**, 6892 (1947).
[21] Smith and Fuzek, *J. Am. Chem. Soc.*, **71**, 415 (1949).
[22] Kucera, Dissertation, The Ohio State University, 1930.
[23] Bradley, *Iowa State Coll. J. Sci.*, **12**, 108 (1937).
[24] Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 4678 (1932).
[25] Guinot (to Les Usines de Melle), U. S. Pat. 2,273,484 (1942); *C. A.*, **36**, 4371 (1942); Usines de Melle and Guinot, French Pat. 811,695 (1937); *C. A.*, **32**, 833 (1938).



The influence of substituent on the direction of hydrogenolysis was further shown by Smith and Fusek[21] who also determined the activation energies of the reaction (Table 1). It can be seen that the direction of hydrogenolysis can be changed from all 1,5-attack in the case of 2-methylfuran to all 1,2-attack in the case of furoic acid.

TABLE 1. HYDROGENOLYSIS OF FURANS OVER PtO_2 IN ACETIC ACID[21]

Compound	Products	Activation energies Cal./mole
Furan	butanol	8,000
2-Methylfuran	2-pentanol 2-methyltetrahydrofuran	8,600
2,5-Dimethylfuran	2-hexanol	10,200
Furoic acid	5-hydroxyvaleric acid tetrahydrofuroic acid	11,400
Furfuryl alcohol	1,2-pentanediol	9,300
Furfural	(stopped at furfuryl alcohol; catalyst poisoned)	4,400

Ease of Hydrogenation. The activation energies increase with the additional resonance energy imparted by substituents capable of entering into resonance with the furan ring. Thus the substituent groups not only can affect the direction of hydrogenolysis but also the resistance of the furan nucleus to attack by hydrogen. This observation is borne out by the semiquantitative work of Kariyone,[26] who evaluated the increasing resistance

[26] Kariyone, *J. Pharm. Soc. Japan*, **515**, 1 (1925); *C. A.*, **20**, 412 (1926).

to hydrogenation of 28 furans over platinum and palladium catalysts. No attempt was made to distinguish hydrogenation of a side group or the ring from hydrogenolysis.

TABLE 2. INCREASING RESISTANCE TO HYDROGENATION OVER Pt AND Pd[26]

Most easily reduced	2-vinylfuran
	3-(2-furyl)acrylic acid
	furfurylideneacetone
	furylphenylmethane
	furfuryl alcohol
	2-furyl methyl ketone
Easily reduced	2-furyl phenyl ketone
	furoin
	furil
	furfuryl ethyl ether
	furfural
	furfural ethyl acetal
	furfurylidene diacetate
Difficultly reduced	furoic acid
	ethyl furoate
	furamide
	furonitrile
	5-nitrofuroic acid
	2,5-furandicarboxylic acid
	dimethyl 2,5-furandicarboxylate
	2-methyl-3-furancarboxylic acid
No reduction	2,5-dimethyl-3-furancarboxylic acid
	2,4-dimethyl-3-furancarboxylic acid
	2,4,5-trimethyl-3-furancarboxylic acid
	2,5-dimethyl-3,4-furandicarboxylic acid
	2,5-diphenyl-3,4-furandicarboxylic acid
	2,5-diphenyl-3-furancarboxylic acid
	5-carboxymethyl-2-methyl-3-furoic acid

A comparison of the rate of hydrogenation of some alkylfurans over palladium showed 2-ethylfuran and 2,5-dimethylfuran more difficult to hydrogenate than 2-methylfuran or furan.[27] Hydrogenation of furfural ethyl acetal over platinum gave complete conversion to the corresponding tetrahydrofuran, but 5-(ethoxymethyl)furfural ethyl acetal gave 27 per cent 5-ethoxymethyl-2-methyltetrahydrofuran and none of the expected 5-(ethoxymethyl)tetrahydrofurfural ethyl acetal.[28] Another example of the

[27] Shuikin, Nikiforov and Stolyarova, *J. Gen. Chem. U. S. S. R.*, **7**, 1501 (1937); *C. A.*, **31**, 8529 (1937).

[28] Moosdorf, Dissertation, Technischen Hochschule zu Darmstadt, Germany, 1930.

effect of substituents on rate of reaction is the observation that 2,5-bis(3-oxobutyl)furan over platinum reacted with hydrogen in 2 hours (forming 2,5,11-dodecanetrione), whereas replacement of an oxobutyl with methyl increased the time necessary for reaction to 84 hours[29] (forming 2,5- and 2,8-nonadione).

Kariyone[26] did not study the effect of basic groups such as amines. These have a marked effect on resistance of the ring to hydrogenation. For instance, Williams[30] was unable to hydrogenate furfurylamine in ether over palladium, but obtained a 45 per cent yield of tetrahydrofurfurylamine when alcoholic hydrochloric acid was used as the medium. With platinum catalyst he was able to reduce the ring if acetic acid (60 per cent yield) or alcoholic hydrochloric acid (81 per cent yield) were used as the medium. This helps to explain the formation of furfurylamine when furfural oxime is hydrogenated over palladium in ether or acetic anhydride, whereas tetrahydrofurfurylamine is produced when working in alcoholic hydrochloric acid. Evidently formation of the ammonium salt overcomes the effect of the free amino group on the resistance of the ring to hydrogenation.

Other workers report similar experiences. Hass, Susie and Heider[31] reduced 1-(2-furyl)-2-propanone to 1-(2-tetrahydrofuryl)-2-propanol over nickel under conditions which converted the oxime to 1-(2-furyl)-2-aminopropane. That the amine need not be part of the furan compound was shown by Bremner, Starkey and Dowden[32] who hydrogenated 2-vinylfuran over nickel to give 2-ethyltetrahydrofuran, but obtained 2-ethylfuran when an aqueous ammonia medium was used. Burger and Harnest[33] reduced 1-furyl-2-piperidino-1-ethanol in the form of the hydrochloride to the corresponding tetrahydrofuran compound under mild conditions. The stabilizing effect of the amine may be overcome by resorting to more strenuous conditions. For instance, furfurylamine can be reduced over nickel to tetrahydrofurfurylamine at 150°,[32] although aqueous ammonia will prevent the reduction even at that temperature. Hydrogenation of the ring of furan-2,5-bispropylamine has been effected at 120–160° over ruthenium catalyst.[34]

Since either an amine or ammonia tends to stabilize the furan ring, the effect can hardly be due to resonance within the furan molecule. Instead, the effect may simply be that of a base on the furan or on the catalyst. The effect of basic media on reaction of furan compounds with hydrogen is not clear. Some of the confusion may be due to differences in effect on side

[29] Alder and Schmidt, *Ber.*, **76**, 183 (1943).

[30] Williams, *Compt rend. acad. sci. U. S. S. R.*, **1930, A**, 523; *C. A.*, **25**, 5163 (1931).

[31] Hass, Susie and Heider, *J. Org. Chem.*, **15**, 8 (1950).

[32] Bremner, Starkey and Dowden (to Imperial Chemical Industries Ltd.), British Pat. 596,880 (1948); *C. A.*, **42**, 4203 (1948).

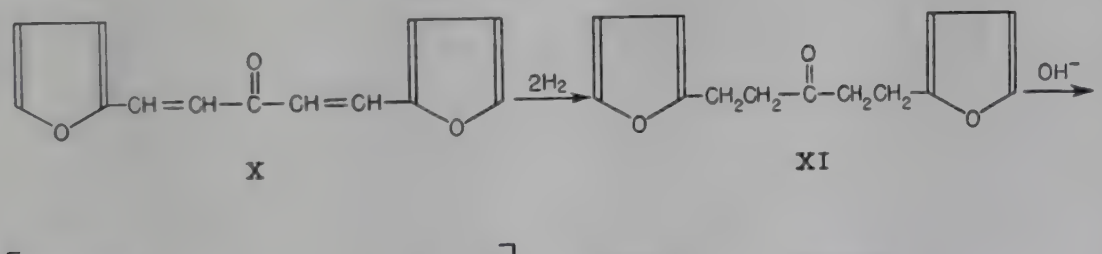
[33] Burger and Harnest, *J. Am. Chem. Soc.*, **65**, 2382 (1943); Burger (to Smith, Kline and French Laboratories), U. S. Pat. 2,400,913 (1946); *C. A.*, **40**, 5455 (1946).

[34] Webb and Borcherdt, *J. Am. Chem. Soc.*, **73**, 752 (1951).

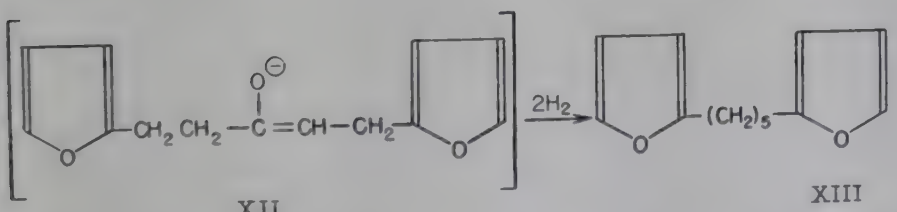
chains, the ring, hydrogenolysis, solvolysis, etc. The velocity of hydrogenation of furan over platinum is said to decrease[35] as the character of the medium is changed from acid to neutral to alkaline. On the other hand, addition of alkalies or alkaline earths to copper catalysts increases the speed of hydrogenation of furfural to furfuryl alcohol; see [12, 14, 11, 10, 36, 37, 38, 39]. A similar effect of sodium hydroxide with nickel catalyst was observed.[6]

Some data on the effect of acidity on hydrogenolysis by copper catalysts indicate that alkalies may reduce the extent of hydrogenolysis. Thus, Bremner[20] reported the formation of tetrahydrofuran in 70 per cent yield from furan in an alkaline medium, which contrasts with the yield of 33 per cent tetrahydrofuran and 10 per cent butanol when using acetic acid as a solvent. Hydrogenation of furfural in the vapor phase over copper was influenced by addition of alkalies to the catalyst such that lesser amounts of 2-methylfuran, due to hydrogenolysis of formed furfuryl alcohol, was noted.[15] The effect of alkali was greatly lessened if the catalyst contained an acidic oxide such as chromium oxide. Bremner and Keeys devised an hypothesis to account for these observations.[15]

The opposite effect of alkali was reported for the hydrogenation of difurfurylideneacetone (X) over nickel. The products were 1,5-difuryl-3-pentanone (XI) in the absence of alkali and 1,5-difurylpentane (XIII) in the presence of sodium hydroxide.[40] That hydrogenolysis seemed to be encouraged by the presence of alkali may have been due to chance for enolization (XII) of the intermediate pentanone. No such enolization would be possible when hydrogenation of furfural is involved.



X XI



XII XIII

[35] Euler, Hasselquist and Lööv, *Arkiv Kemi Mineral. Geol.*, **25B**, No. 10, 6 pp. (1948); *C. A.*, **42**, 5896 (1948).

[36] Connor, Folkers and Adkins, *J. Am. Chem. Soc.*, **54**, 1138 (1932).

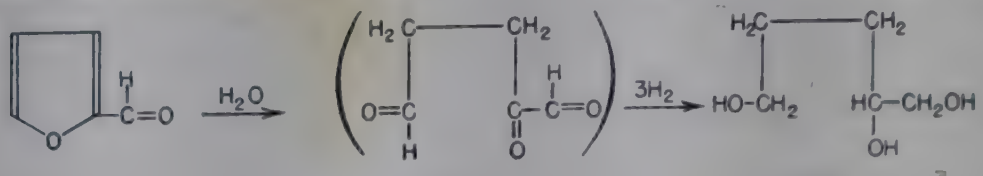
[37] Röhm and Haas Co., British Pat. 410,148 (1934); *C. A.*, **28**, 6157 (1934).

[38] Adkins and Connor (to The Quaker Oats Co.), U. S. Pat. 2,094,975 (1937); *C. A.*, **31**, 8549 (1937).

[39] Peters (to The Quaker Oats Co.), U. S. Pats. 1,903,850 and 1,906,873 (1933); *C. A.*, **27**, 3224, 3486 (1933).

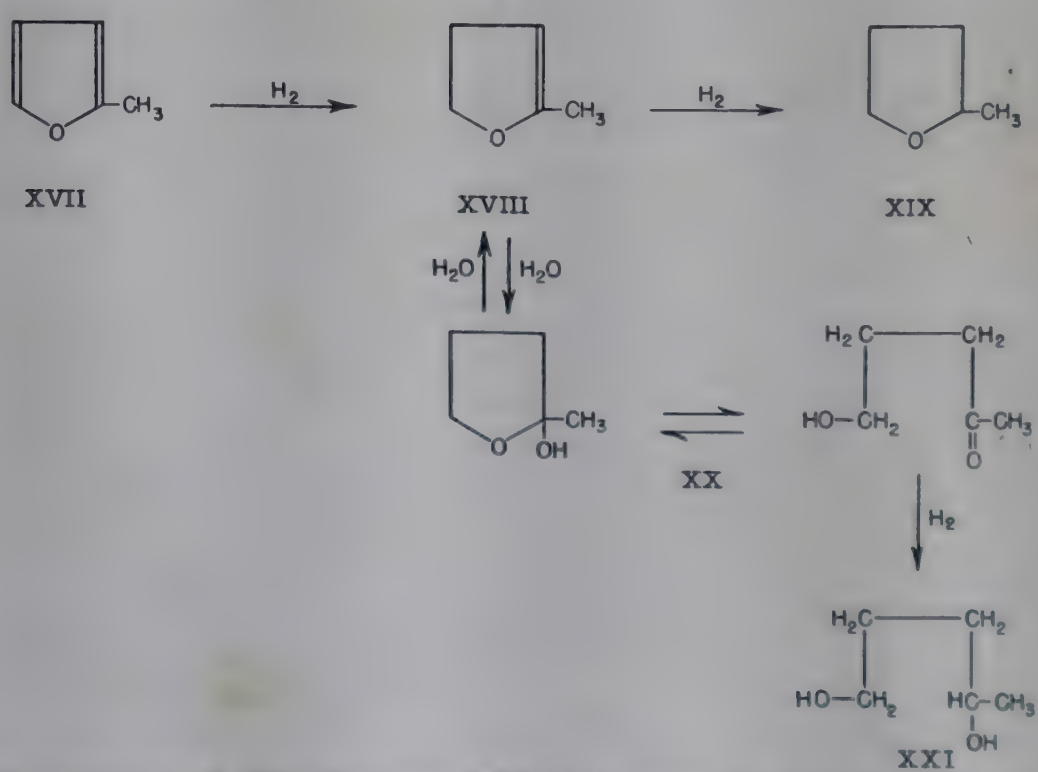
[40] Cornubert and Phélisse, *Compt rend.*, **229**, 460 (1949).

Solvolysis. The acidity of the medium during hydrogenation is especially important in another competing reaction; namely, solvolysis. As has been discussed elsewhere (Chapter 14), the furan ring may be opened hydrolytically. If furfural (XIV) is hydrogenated, and especially in an acidic aqueous medium, 1,2,5-pentanetriol (XVI) may be found among the products.[41] One might account for the occurrence of the triol as resulting from hydrogenation of the hydrolytically opened furan ring (XV). However, the furan



XIV XV XVI

ring of furfural is not appreciably opened by aqueous acid of the concentration and under the conditions which are suitable for the above reaction. The first clue to the actual mechanism involved may be seen in the work of Topchiev[42, 43] who reported 5-hydroxy-2-pentanone as a product from the partial hydrogenation of 2-methylfuran over a nickel or palladium catalyst in the presence of water. Palladium was described as a "specific catalyst" for the reaction. No experimental details were reported but a mechanism was suggested which involved dihydrogenation of 2-methylfuran to 2-methyl-4,5-dihydrofuran (XVIII), which was competitively hydrated to XX or hydrogenated to XIX. Further hydrogenation of XX would account for 1,4-pentanediol (XXI), which was also isolated from the reaction products.

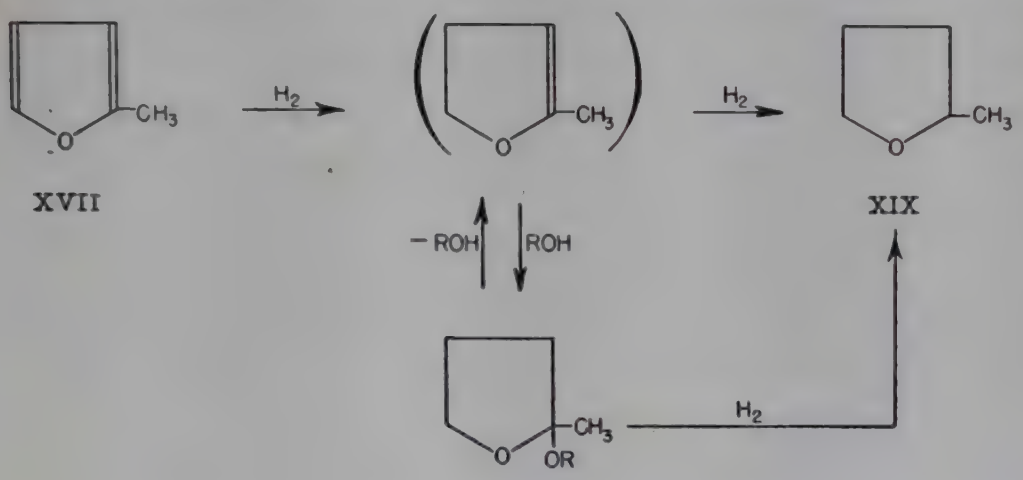


XVII XVIII XIX XX XXI

The existence of dihydrofuran (XVIII) might be surprising in view of

the resonance energy of the furan ring (page 6) which calls for a much higher activation energy for XVII → XVIII than would be required for XVIII → XIX. However, it is reasonable that the reaction XVII → XIX should be stepwise since it is statistically unlikely that a molecule of XVII could react simultaneously with two of hydrogen. Proof of the existence of XVIII as a transitory intermediate may be seen from the following considerations.

Schniepp, Geller and Von Korff[44] made an intensive study of the reaction and established the conditions necessary to obtain 5-hydroxy-2-pentanone (XX) from 2-methylfuran; hydrogenation over a nickel catalyst in presence of traces of formic acid promoted the reaction. If Topchiev's mechanism is valid, the effect of the acid would be to catalyze the addition of water to an enol ether (XVIII). Additional evidence for the dihydrogenation mechanism was later obtained[45] from a study of the reaction conducted in acidic alcoholic media, which resulted in formation of 2-methyl-2-alkoxytetrahy-



drofuran (XXII). No 1,4-pentanediol was found. Evidently XXII is not hydrolyzed to hydroxypentanone (XX) in the alcoholic system and if further reaction occurs, it is hydrogenolysis to 2-methyltetrahydrofuran (XIX), for instance. A rough kinetic study of the reaction rates of the starting compound, as well as the intermediates is shown in Table 3.

Without the trace of acid, XVIII reacts much more rapidly than XVII does and this accounts for the usual inability to isolate a dihydrofuran as an hydrogenation product. However, in the presence of an acid, the apparent rates of hydrogenation of XVII and XVIII become nearly identical, prob-

[41] Leuck, Pokorny and Peters (to The Quaker Oats Co.), U. S. Pat. 2,097,493 (1937); *C. A.*, **32**, 193 (1938).

[42] Topchiev, *Compt rend. acad. sci. U. R. S. S.*, **19**, 497 (1938); *C. A.*, **32**, 8411 (1938); *Ann. secteur platine Inst. chim. gen. U. S. S. R.*, **19**, 60 (1943); *C. A.*, **38**, 2334 (1944).

[43] Topchiev and Pavlov, Russian Pat. 48,104 (1937); *C. A.*, **31**, 8549 (1937).

[44] Schniepp, Geller and Von Korff, *J Am. Chem. Soc.*, **69**, 672 (1947).

[45] Swadesh, Smith and Dunlop, *J. Org. Chem.*, **16**, 476 (1951).

TABLE 3. PER CENT REACTED WITH HYDROGEN[45]
(Reaction conditions constant)

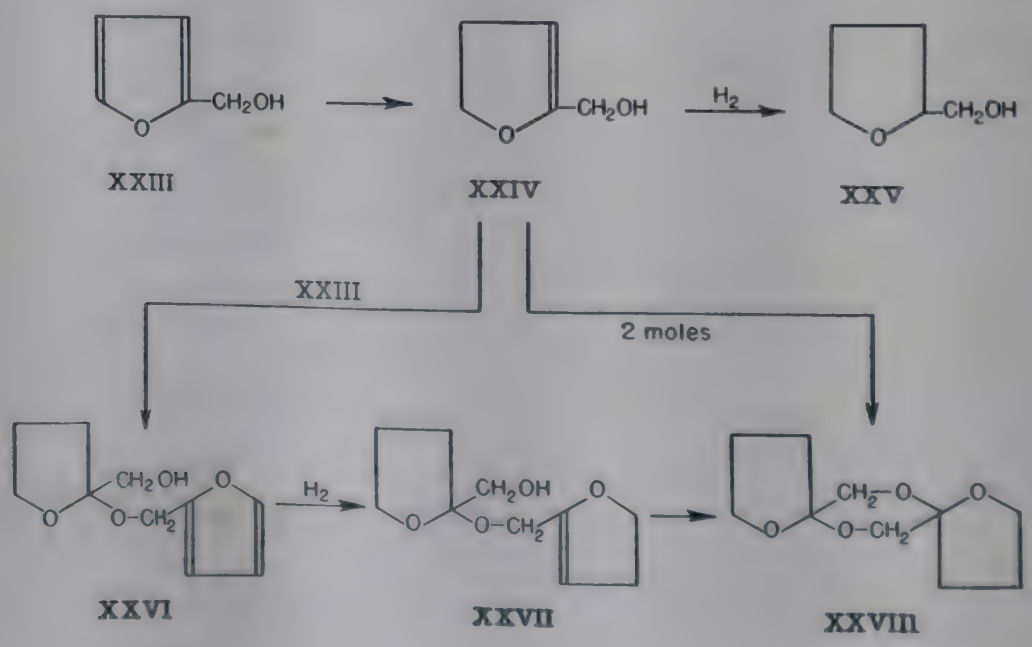
Compound	Without acid (%)	With acid (%)
2-Methylfuran (XVII)	88	90
2-Methyl-4,5-dihydrofuran (XVIII)	130*	87
5-Hydroxy-2-pentanone (XX)	75	55
2-Methyl-2-methoxytetrahydrofuran (XXII)	28	42

* 98 per cent, in ¾ of the time used on the other runs.

ably due to competitive formation of XXII by acid-catalyzed addition of alcohol to the enol ether, XVIII. Note that the rate of hydrogenation of XVII is unaffected by the trace of acid. Opposite effects of acid on the rates of hydrogenation of XX and XXII are observed. Acid catalyzes the conversion of XX to the more stable form, XXII. On the other hand, acid increases the rate of hydrogenation of XXII, probably by catalyzing the reversal reaction to the more easily hydrogenated dihydrofuran (XVIII). Thus, the concentration of acid is highly critical: an insufficient amount reduced the formation of the protected alkoxytetrahydrofuran, while an excess may favor reversal to the dihydrofuran, XVIII. In addition, excess acid may promote hydrogenolysis of the acetal (XXII) to the tetrahydrofuran (XIX).

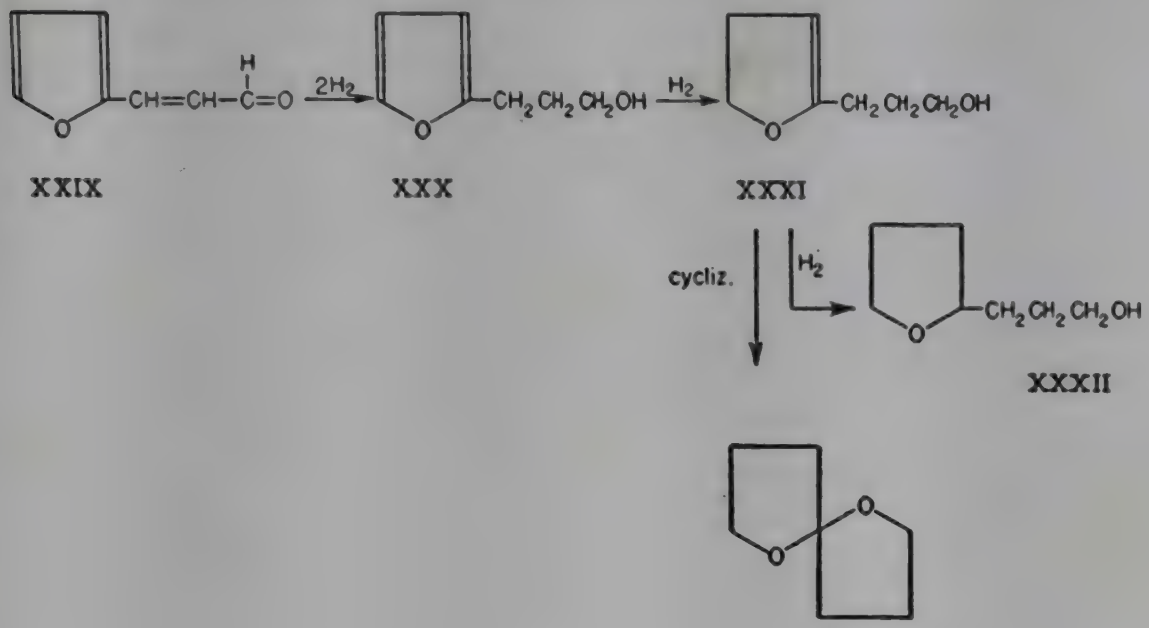
Similarly, time was found to be a critical factor. Other variables, although not studied, also must play an important role in the relative yields obtained in the reaction.

The dihydrogenation mechanism has been used to account for a minor by-product, 2,5-bis(trimethyleneoxy)-1,4-dioxane (XXVIII), obtained from commercial hydrogenation of furfuryl alcohol to tetrahydrofurfuryl alcohol.[46]



Since XXIV has both an enol ether and an alcohol group, dimerization to XXVIII could occur, although it is more likely that the reaction follows the route through XXVI and XXVII.

Another by-product, 1,9-dioxa-5-spirononane (XXXIII), formed during hydrogenation of 3-(2-furyl)acrolein[47, 48] can be explained on a similar basis,



XXIX XXX XXXI

XXXII

XXXIII

namely, by way of XXX and XXXI. It was originally thought[47] that the bicyclization did not occur through the furylpropanol (XXX) since the

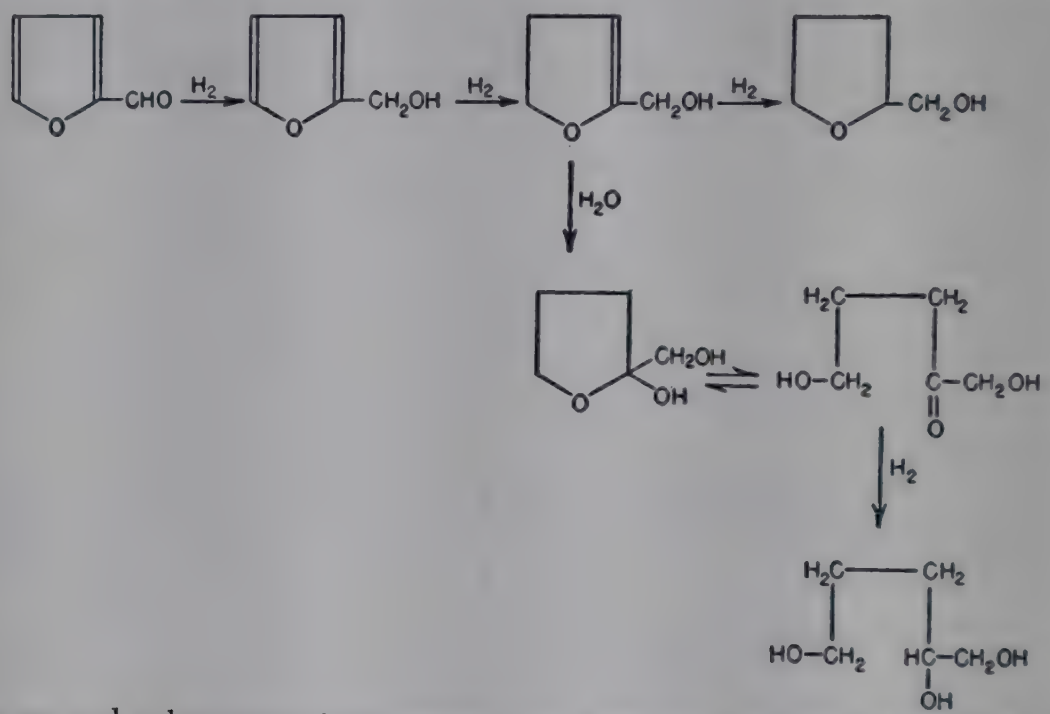
TABLE 4. SPIRONONANES FROM HYDROGENATION OF FURANS

Compound	Catalyst	Spirononane (yield)	Ref.
3-(2-Furyl)acrolein	Ni(R)	1,9-dioxa-5- (3%)	47
3-(2-Furyl)acrolein	Ni(K)	1,9-dioxa-5- (33%)	47
3-(2-Furyl)acrolein	Ni(R)	1,9-dioxa-5- (12%)	49, 18
2-Ethyl-3-(2-furyl)acrolein	Ni(R)	3-ethyl-1,9-dioxa-5- (10%)	18
3-(2-Furyl)-2-(methoxymethyl)acrolein	Ni	3-methyl-1,9-dioxa-5- (50%)	50
3-(2-Furyl)-2-(tetrahydrofurfuroxymethyl)acrolein	Cr-Ni	3-methyl-1,9-dioxa-5- (30%)	50
Furfurylideneacetone	Ni(R)	2-methyl-1,9-dioxa-5- (—)	18
Furfurylideneacetone	Cu-CrO	2-methyl-1,9-dioxa-5- (10%)	51
Difurfurylideneacetone	Cu-CrO	2-(2-(2-furyl)ethyl)-1,9-dioxa-5- (15–25%)	51
Diethyl (2-furfurylidene)-malonate	Ni(R)	3-carbethoxy-1,9-dioxa-5- (—)	18

[46] Swadesh and Dunlop, *J. Org. Chem.*, **14**, 692 (1949).
[47] Burdick and Adkins, *J. Am. Chem. Soc.*, **56**, 438 (1934).
[48] Farlow, Burdick and Adkins, *J. Am. Chem. Soc.*, **56**, 2498 (1934).

latter (hydrogenated over Raney nickel) gave only 3 per cent of XXXIII, whereas a 33 per cent yield was obtained from the furylacrolein (hydrogenated over nickel-on-kieselguhr). However, as later shown,[45] the sensitivity of the reaction to traces of acids is such that the difference in acidity of the two types of nickel catalyst accounts for the differences in yield. Actually, when XXIX is hydrogenated over Raney nickel, only a 3 per cent yield of XXXIII was obtained.[47] A number of other spirononanes have been reported from hydrogenation of furan compounds and are shown in Table 4.

Consideration of these findings suggests that the formation of 1,2,5-pentanetriol from furfural[41] proceeds in related fashion and involves a combined dihydrogenation-hydration sequence (below) rather than hydrolytic



cleavage and subsequent hydrogenation. Attempts to extend the technique of hydrogenation in an acidic, aqueous medium to other furans gave variable results.[44] From furan, tetrahydrofuran but no diols were obtained; nor were triols obtained from furfuryl alcohol. A small yield of 1,4-dihydroxypentyl acetate was obtained from furfuryl acetate; 2-vinylfuran gave 37 per cent of 1,4-hexanediol, the remaining product being 2-ethyltetrahydrofuran.

It is conceivable, although proof is lacking, that hydrogenolysis of the furan ring also involves the intermediate formation of a dihydrofuran; that hydrogenolysis of the latter rather than hydrogenolysis of the resonance-stabilized furan ring is the route of the ring opening.

Selective Hydrogenation. All other variables aside, the chemical properties of the various parts of a given furan molecule will determine the selectivity

[49] Hinz and Meyer, "Degradation Reactions of Hydrogenated Furfural Condensation Products", PB No. **52009**, U. S. Dept. Commerce, 1941; *C. A.*, **41**, 5124 (1947).

[50] Hinz and Laberenz, "On Some Furan Derivatives and Their Catalytic Hydrogenation," PB No **19416**, U. S. Dept. Commerce, 1944.

[51] Alexander, Hafner, Smith and Schniepp, *J. Am. Chem. Soc.*, **72**, 5506 (1950).

of hydrogenation which may be obtained; the influence of these properties will now be considered.

The resonance energy of furan, although appreciable, is less than that of benzene and in general, furans possessing a phenyl group may be reduced selectively. A typical example is the hydrogenation of 2-benzylfuran over nickel to 2-benzyltetrahydrofuran.[52] Rate constants for hydrogenation of a series of furans and their benzene analogs showed the rate constant for the furan was from 1.3 to 3.8 times as great as the rate constant for its benzene analog. The furan ring is also more easily reduced over nickel than is an ester group. Thus methyl furoate is hydrogenated in good yield to methyl tetrahydrofuroate.[53]

Less stable substituents such as vinyl or aldehyde groups are attacked before the furan ring. Thus, 2-vinylfuran can be changed by hydrogenation over nickel into 2-ethylfuran,[54] although vigorous conditions, such as the use of pressures over 250 atmospheres, give rise to 2-ethyltetrahydrofuran. Furfural may be preferentially hydrogenated over nickel to furfuryl alcohol, if the temperature is kept below about 125°. At higher temperature, tetrahydrofurfuryl alcohol will be formed. For this reason, the preferred catalyst for commercial production of furfuryl alcohol is copper-chromite, which does not affect the ring below about 200°.

Some estimations of heats of hydrogenation and free energy change for hydrogenation of several furans have been made, and are shown in Table 5. These are indicative of the relative stabilities of the groups involved.

In order to hydrogenate the ring of furfural selectively to prepare tetrahydrofurfural, some means must be found to protect the aldehyde group

TABLE 5. HEATS OF HYDROGENATION OF FURANS

Reactant	Product	ΔH 298° Heat of hydrogenation Cal./mole	ΔF 298° Free energy change Cal./mole	Ref.
Furan	tetrahydrofuran	−36,630	—	55
Furfural	furfuryl alcohol	−18,500 (from combustion data)		15
		−17,600 (from bond energy data)	−13,181	15 56
Furfuryl alcohol	tetrahydrofurfuryl alcohol	−36,120	−17,755 −17,765	56 57
Furfural	2-methylfuran	−34,000	—	15
Furfural	1,5-pentanediol	—	−31,731	56

[52] Paul, *Compt. rend.*, **202**, 1444 (1936).

[53] Wilson, *J. Chem. Soc.*, **1945**, 58.

[54] Bremner (to Imperial Chemical Industries Ltd.), British Pat. 627,492 (1949); *C. A.*, **44**, 2565 (1950).

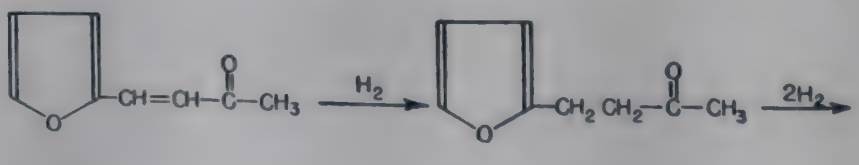
[55] Dolliver, Gresham, Kistiakowsky, Smith and Vaughan, *J. Am. Chem. Soc.*, **60**, 440 (1938).

in a form more resistant to hydrogenation than is the furan ring. The reduction of furfural ethyl acetal to tetrahydrofurfural ethyl acetal[28] over platinum has already been mentioned. The saturated acetal can then be hydrolyzed, albeit in poor yield, to tetrahydrofurfural. When hydrogenation of furfural ethyl acetal was attempted over nickel,[58] complete conversion to 2-(ethoxymethyl)tetrahydrofuran occurred, i.e., one of the ethoxy groups was detached by hydrogenolysis. Addition of a small amount of pentylamine corrected this difficulty and a 76 per cent yield of the desired acetal was achieved. The reaction also has been carried out over palladium.[59]

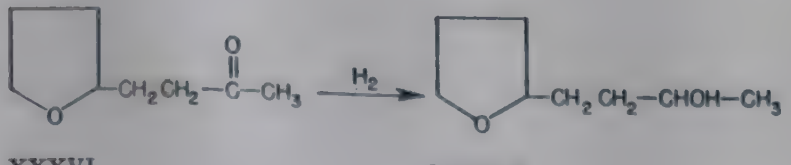
The cyclic acetal from furfural and ethylene glycol has been hydrogenated over Raney nickel with a 96 per cent yield of tetrahydrofurfural ethylene acetal.[18] Furfural 2-ethoxyethyl acetal was hydrogenated over nickel to give a 69 per cent yield of tetrahydrofurfural 2-ethoxyethyl acetal and 7 per cent of furfuryl 2-ethoxyethyl ether due to hydrogenolysis.[60]

Another approach to the selective hydrogenation of the furan ring of furfural has been via protection of the aldehyde group as an acylal. Furfural diacetate over palladium formed 75 per cent of tetrahydrofurfural diacetate.[59] Hydrogenation over nickel gave only a 24 per cent yield of tetrahydrofurfural diacetate and 51 per cent yield of hydrogenolysis products, mainly tetrahydrofurfuryl acetate with some 2-methyltetrahydrofuran.[47] However, much of the desired acylal was lost in the course of isolation by distillation. The yield of tetrahydrofurfural diacetate from hydrogenation of furfural diacetate over nickel can be raised to 80 per cent, if care is taken to distill the reaction products quickly, in small batches and under high vacuum.[61] When hydrogenation of furfural diacetate over nickel was conducted in ether, hydrogenolysis was extensive and an 82 per cent yield of furfuryl acetate was obtained.[18]

The furfurylidene compounds obtained from condensation of furfural with active methylene groups are interesting to consider, since selective hydrogenation involves at least three susceptible groups. Furfurylideneacetone has been shown to hydrogenate stepwise over platinum.[17]



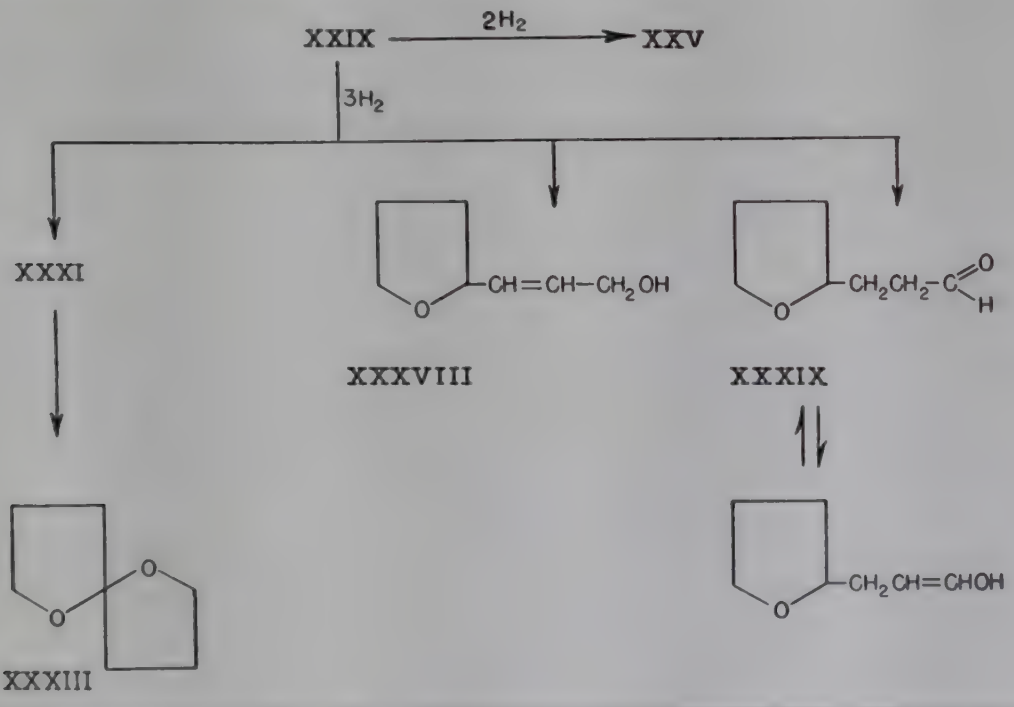
XXXIV XXXV



XXXVI XXXVII

As might be expected, the ethylene bond is hydrogenated first, but contrary to the relative stabilities of the furan ring and the carbonyl group, the ring is attacked before the carbonyl group. This order of things may be peculiar to platinum as a catalyst and the known difficulty of reduction of carbonyl groups over platinum. At any rate, 4-(2-tetrahydrofuryl)-2-butanone (XXXVI) has never been reported from the hydrogenation of furfurylideneacetone over nickel, except in one patented instance,[39] in which very crude cuts of distillate were obtained and no actual identification was made of the claimed product. In a related experiment, 2-(2-tetrahydrofuryl)ethyl isobutyl ketone was reported from hydrogenation of 2-(2-furyl)vinyl isobutyl ketone over nickel.[62] However, the ketonic nature of the product is questionable, since the author was unable to prepare a semicarbazone.

With 3-(2-furyl)acrolein, the order of hydrogenation is ethylene, carbonyl, and then ring. If zinc, a selective poison, is used with platinum, the hydrogenation of furylacrolein stops after reduction of the aldehyde group to form 3-(2-furyl)propenol.[4] Bray and Adams[4] reported a by-product from hydrogenation of furylacrolein (XXIX) over platinum (and in the absence of zinc), which they tentatively characterized as 3-(2-tetrahydrofuryl)propenol (XXXVIII) which would call for the ethylene group to be more stable than the furan ring. Such a behavior is extremely unlikely and reëxamination of the product is in order.



[56] Miller, *Iowa State Coll. J. Sci.*, **10**, 91 (1935).
[57] Mattei, *Ricerca sci.*, **13**, 783 (1942); *C. A.*, **39**, 2024 (1945).
[58] Covert, Connor and Adkins, *J. Am. Chem. Soc.*, **54**, 1651 (1932).
[59] Scheibler, Sotscheck and Friese, *Ber.*, **57**, 1443 (1924); **58**, 1961 (1925).
[60] Minné and Adkins, *J. Am. Chem. Soc.*, **55**, 299 (1933).
[61] The Quaker Oats Company, unpublished work.

The analyses agreed with XXXVIII. Bray and Adams rejected XXXI on the grounds of chemical improbability. They were unable to make a naphthylurethan or a dinitrobenzoate derivative but were able to form a liquid acetate, which analyzed correctly, and on that basis assigned structure XXXVIII to the compound. The formation of a monoacetate, as well as the physical constants, rules out the spirononane (XXXIII). A possibility, which was not considered, is that the compound has the aldehyde structure XXXIX. Since the "acetic ester" might be a vinyl ether, this evidence is not critical. The non-formation of other alcohol derivatives supports this suggestion. Furthermore, the occurrence of XXXIX can be explained in a manner similar to that discussed regarding furfurylideneacetone, namely, if the carbonyl group poisoned the platinum catalyst towards carbonyl reduction before hydrogenation of the carbonyl group was completed, part of the reaction might involve selective hydrogenation of the ethylene bond and of the furan ring, resulting in the formation of XXXIX.

With an unsaturated ester such as ethyl 3-(2-furyl)acrylate, first the ethylene position is attacked and then the ring, leaving the ester group intact. Ethyl 3-(2-tetrahydrofuryl)propionate is formed.[63, 64] Four functional groups are involved in ethyl furfurylideneacetoacetate and only the ethylene, carbonyl and ring are hydrogenated to give ethyl 2-(tetrahydrofuryl)-3-hydroxybutanoate.[63]

Where a phenyl group is involved, as with furfurylideneacetophenone, the ethylene, carbonyl and furan ring will be hydrogenated without affecting the benzene ring. Thus, 3-(2-tetrahydrofuryl)-1-phenyl-1-propanol was reported[17] as the principal product.

Furan and Its Homologs

Hydrogenation of furan over platinum gives both tetrahydrofuran and butanol.[22] The latter may be the only product if the reaction is conducted in acetic acid.[21] Palladium causes no hydrogenolysis,[65] even at 170°,[27] nor does osmium at 70°.[66] Raney nickel causes hydrogenation of furan to tetrahydrofuran in high yield at temperatures from 80–140°[67, 68, 69, 70, 71,

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[62] Wienhaus and Leonhardi, *Ber. Schimmel & Co., Akt. Ges.*, **1929**, 225; *C. A.*, **24**, 2127 (1930).

[63] Paul and Hilly, *Compt. rend.*, **208**, 359 (1939).

[64] Kleene, *J. Am. Chem. Soc.*, **68**, 718 (1946).

[65] Starr and Hixon, "Organic Syntheses," Vol. 16, p. 77, New York, John Wiley & Sons, Inc. (1936).

[66] Shuikin and Chilikina, *J. Gen. Chem. U. S. S. R.*, **6**, 279 (1936); *C. A.*, **30**, 4855 (1936).

[67] Cloke and Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).

[68] Cloke and Ayers, *J. Am. Chem. Soc.*, **56**, 2144 (1934).

[69] Codignola and Piacenza, Italian Pat. 439,947 (1948); *C. A.*, **44**, 5915 (1950).

[72, 55, 73] or in the vapor phase.[74] Nickel, on kieselguhr or pumice, is also effective,[75, 76, 77] but at temperatures from 150 to 200°. Copper catalysts may be used for the preparation of tetrahydrofuran but the temperatures required (from 220 to 300°) are so high that considerable hydrogenolysis may result.[20] A 20 per cent yield of butadiene is reported from hydrogenation of furan in the vapor phase over copper.[78]

Similar results are obtained with the alkylfurans. Platinum in acetic acid causes almost complete hydrogenolysis of 2-methylfuran or 2,5-dimethylfuran,[21] and in the absence of acetic acid a mixture of octahydro-2,2′-bifuryl and 1,8-octanediol is formed from 2,2′-bifuryl.[79]

No evidence has been reported for hydrogenolysis when using palladium on 2-methylfuran,[27] 2,5-dimethylfuran,[80, 27] 2-propylfuran[82] or 5-methyl-2-ethylfuran.[82] Each of these alkylfurans gave rise to the corresponding alkyltetrahydrofuran. Osmium allows complete hydrogenation of 2-methylfuran into 2-methyltetrahydrofuran.[83] Raney nickel largely favors hydrogenation to the alkyltetrahydrofuran of 2-methylfuran in the liquid phase[70, 84] or in the vapor phase,[85, 74] and of 2-ethylfuran[86] or 2,5-dimethylfuran.[67] The same catalyst allows conversion of 2,2′-bifuryl to octahydro-2,2′-bifuryl.[87] Nickel on pumice induces nearly quantitative hydrogenation of 2-methylfuran and 2,5-dimethylfuran,[75] but other forms of nickel allowed

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[70] Shuikin and Bunina, *J. Gen. Chem. U. S. S. R.*, **8**, 669 (1938); *C. A.*, **33**, 1316 (1939).

[71] Tarbell and Weaver, *J. Am. Chem. Soc.*, **63**, 2939 (1941).

[72] Heisig, *J. Am. Chem. Soc.*, **61**, 525 (1939).

[73] E. I. du Pont de Nemours & Co. and Lazier, British Pat. 428,940 (1935); *C. A.*, **29**, 6903 (1935).

[74] Bremner and Starkey (to Imperial Chemical Industries Ltd.), British Pat. 630,863 (1949).

[75] Bolcs, Hungarian Pat. 132,763 (1944); *C. A.*, **43**, 4301 (1949).

[76] Lazier (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,033,292 (1936); *C. A.*, **30**, 2994 (1936).

[77] Bourgignon, *Bull. soc. chim. Belgique*, **22**, 87 (1908); *Chem. Centr.*, **1908**, **I**, 1630.

[78] Yur'ev, Tronova, Kuznetsova and Novosadova, *J. Gen. Chem. U. S. S. R.*, **17**, 131 (1947); *C. A.*, **42**, 164 (1948).

[79] Kondo, Suzuki and Takeda, *J. Pharm. Soc. Japan*, **55**, 741 (1935); *C. A.*, **29**, 7324 (1935).

[80] Yur'ev, Tronova, L'vova and Bukshpan, *J. Gen. Chem. U. S. S. R.*, **11**, 1128 (1941); *C. A.*, **37**, 4071 (1943).

[82] Shuikin, Shemastina and Cherkasova, *J. Gen. Chem. U. S. S. R.*, **8**, 674 (1938); *C. A.*, **33**, 1316 (1939).

[83] Zelinskii and Shuikin, *Compt. rend. acad. sci. U. R. S. S. (N. S.)*, **1933**, 60; *C. A.*, **28**, 2002 (1934).

[84] Burnette, *Iowa State Coll. J. Sci.*, **19**, 9 (1944); *Rubber Chem. Tech.*, **18**, 460 (1945).

[85] Johns (to Iowa State College Research Foundation) U. S. Pat. 2,458,001 (1949); *C. A.*, **43**, 2805 (1949).

[86] Paul, *Bull. soc. chim.* (*5*), **5**, 1053 (1938).

[87] Fieser, Fry and Jones, *J. Am. Chem. Soc.*, **61**, 1849 (1939).

small amounts of hydrogenolysis to occur during hydrogenation of 2-methylfuran.[76, 25]

As was true with furan, copper catalysts had to be used with methylfuran at very high temperatures, hence considerable hydrogenolysis occurred.[20] In the vapor phase, copper at 300° to 350° almost exclusively catalyzed hydrogenolysis of 2-methylfuran to 2-pentanone[9, 88] or 2-ethylfuran to 2-hexanone.[88] Since, at the temperatures employed, copper acts as a dehydrogenation catalyst, it is reasonable to find the hydrogenolysis product a ketone rather than an alcohol.

The alkenylfurans may be selectively hydrogenated in the side chain if gentle conditions are used. Nickel at low temperatures, and in the presence of an amine, allows hydrogenation of 2-vinylfuran to 2-ethylfuran in over 80 per cent yields.[32, 89, 54] Platinum allows selective hydrogenation of the double bond in 2-isopropenylfuran,[90] 2-(2-furyl)-2-butene,[91] 5-(3-furyl)-2-methyl-2-pentene[92] or 1-phenyl-2-(2-furyl)ethylene.[93] Even in the vapor phase at 330° and over copper, 67 per cent yield of 2-ethylfuran from 2-vinylfuran has been realized,[94] presumably by attention to contact time.

Hydrogenation of alkenylfurans with nickel or palladium, conducted so that the furan ring as well as the side chain is reduced, has been successful, except in one experiment. In that run, acetic acid was used as the solvent and extensive hydrogenolysis of 5-(3-furyl)-2-methyl-2-pentene[92] occurred, to form 2-ethyl-6-methyl-1-heptanol. With the other compounds (shown in Table 6) no hydrogenolysis was reported. An interesting example of how pressure may influence the selectivity of a catalyst is that in which hydrogenation of 2-vinylfuran over nickel at 65° led to 2-ethylfuran at less than 250 atmospheres of pressure, but yielded 2-ethyltetrahydrofuran at higher pressures.[54]

Hydroformylation ("oxo" reaction) of furan at 125° had been attempted

[88] Bremner, Jones and Coats (to Imperial Chemical Industries Ltd.), U. S. Pat. 2,537,813 (1951); *C. A.*, **45,** 3411 (1951).

[89] Bremner, Starkey and Dowden (to Imperial Chemical Industries Ltd.), U. S. Pat. 2,519,631 (1950).

[90] Reichstein, Zschokke, Gehring and Rona, *Helv. Chim. Acta*, **15,** 1118 (1932).

[91] Gilman and Calloway, *J. Am. Chem. Soc.*, **55,** 4197 (1933).

[92] Kondo and Suzuki, *Ber.*, **69,** 2459 (1936); Kondo and Yamaguchi, *J. Pharm. Soc. Japan*, **446,** 263 (1919); *C. A.*, **13,** 1617 (1920); Suzuki, *Ibid.*, **56,** 841 (1936); *C. A.*, **33,** 552 (1939).

[93] Woodward, *J. Am. Chem. Soc.*, **62,** 1478 (1940).

[94] Jones (to Imperial Chemical Industries Ltd.), British Pat. 621,744 (1949); *C. A.*, **44,** 3030 (1950).

[95] Yur'ev and Gragerov, *Zhur Obschei Khim. J. Gen. Chem.*, **19,** 724 (1949); *C. A.*, **44,** 1092 (1950).

[96] Shuikin and Daiber, *Bull. acad. sci. U. R. S. S. Classe sci. chim.*, **1941,** 121 *C. A.*, **37,** 3087 (1943).

[97] St. Pfau, Pictet, Plattner and Susz, *Helv. Chim. Acta*, **18,** 935 (1935).

TABLE 6. COMPLETE HYDROGENATION OF ALKENYL- AND ARALKYLFURANS

Compound	Catalyst	Tetrahydrofuran	Ref.
2-Vinylfuran	Ni	2-ethyl-	32
2-Vinylfuran	Pd	2-ethyl-	95
3-Vinylfuran	Pd	3-ethyl-	95
2-Propenylfuran	Pd	2-propyl-	95, 96
2-Propenylfuran	Ni(R)	2-propyl-	86
(2-Furyl)cyclopropane	Pd	2-propyl-	95
3-Propenylfuran	Pd	3-propyl-	95
2-(1-Butenyl)furan	Ni(R)	2-butyl- (68% yield)	86
2-(1-Butenyl)furan	Pd	2-butyl-	95
1-Methyl-2-(2-furyl)cyclopropane	Pd	2-butyl-	96
2-(1-Pentenyl)furan	Ni(R)	2-pentyl- (50% yield)	86
3-(4-Methyl-3-pentenyl)furan	Pd	3-(4-methylpentyl)-	92
1-(2-Furyl)-2-benzylacetylene	Ni	2-(3-phenylpropyl)-	97
2-Benzylfuran	Ni(R)	2-benzyl- (91% yield)	86
2-Benzylfuran	Ni	2-benzyl-	52

by Adkins and Krsek[98] but no apparent reaction occurred. Orchin[99] (see also [99a]) found that at higher temperatures (160–180°) hydroformylation and simultaneous hydrogenation of furan occurred to give a 35 per cent yield of tetrahydrofurfuryl alcohol. Similar treatment of 2,5-dimethylfuran gave 2,5-dimethyl-3-tetrahydrofurylcarbinol. With 2-vinylfuran, Adkins[98] observed a 50–75 per cent uptake of hydrogen and carbon monoxide but was unable to isolate an aldehyde as a product; and when ethyl 3-(2-furyl)-acrylate was subjected to similar conditions, a double bond was hydrogenated to form ethyl 3-(2-furyl)propionate.

FURFURAL AND FURFURYL ALCOHOL

The hydrogenation of furfural to furfuryl alcohol has not only been of interest as a problem in selective hydrogenation but also because of the commercial importance of furfuryl alcohol. The preferred commercial catalyst is copper-chromite with an added alkaline earth oxide. The latter increases the activity of the catalyst, and reduces any tendency for hydrogenolysis or resinification of the formed furfuryl alcohol. By the use of copper-chromite, at temperatures below 200°, furfural has been hydrogenated to furfuryl alcohol in yields well above 90 per cent.[37, 38, 100, 8, 101, 102,

[98] Adkins and Krsek, *J. Am. Chem. Soc.*, **71**, 3051 (1949).

[99] Wender, Levine and Orchin, *J. Am. Chem. Soc.*, **72**, 4375 (1950).

[99a] E. I. du Pont de Nemours & Co., British Pat. 614,010 (1948); *C. A.*, **43**, 4685 (1949).

[100] Salzberg (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,129,507 (1938); *C. A.*, **32**, 8716 (1938).

[103, 69, 104, 105] Other copper catalysts have been used but, except for Raney copper in a continuous process,[106, 107] the yields of furfuryl alcohol have not been satisfactory.[108, 109] Raney cobalt was a poor catalyst for continuous hydrogenation of furfural to furfuryl alcohol,[106, 107] but cobalt plus sodium carbonate used in batch hydrogenation is reported to give a 90 per cent yield of furfuryl alcohol.[110]

Nickel catalysts may be used for the hydrogenation of furfural to furfuryl alcohol, but care must be taken to avoid reduction of the formed furfuryl alcohol to 2-methylfuran or further hydrogenation leading to reduction of the furan ring,[75, 39, 111, 112, 113, 114, 115] which impairs the yield.

A platinum catalyst has been used for hydrogenation to furfuryl alcohol in a 90 per cent yield.[17]

Several substituted furfurals have been catalytically hydrogenated to the corresponding furfuryl alcohols: 5-methylfurfural over platinum[116] and over copper-chromite,[117] and 5-(hydroxymethyl)furfural over Raney nickel.[118]

Considerable effort has been expended on vapor phase hydrogenation of furfural to furfuryl alcohol because of the desire to be able to use a continuous process at near-atmospheric pressures. Copper catalysts have been used mainly to avoid hydrogenation of the nucleus. However, further reduction of the furfuryl alcohol to 2-methylfuran may interfere seriously. Thus, over

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[101] Lazier (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,137,407 (1938); *C. A.*, **33**, 1758 (1939).

[102] Katsuno, *J. Soc. Chem. Ind. Japan*, **46**, 114, 859 (1943); *Ibid.*, **47**, 103 (1944); *C. A.*, **43**, 1718 (1949).

[103] Katsuno, *Bull. Chem. Soc. Japan*, **21**, 69 (1949); *C. A.*, **44**, 1476 (1950).

[104] Calingaert and Edgar, *Ind. Eng. Chem.*, **26**, 878 (1934).

[105] Roberti, *Ann. chim. applicata*, **25**, 530 (1935).

[106] Starkey and Bremner (to Imperial Chemical Industries Ltd.), British Pat. 627,293 (1949); *C. A.*, **44**, 2564 (1950).

[107] Imperial Chemical Industries Ltd., French Pat. 940,692 (1948).

[108] Graves (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,077,049 (1937); *C. A.*, **31**, 3944 (1937).

[109] Sugino and Furumi, *J. Chem. Soc. Japan*, **62**, 1057 (1941); *C. A.*, **41**, 3092 (1947); Sugino and Mizuguchi, *Ibid.*, **64**, 1385 (1943); *C. A.*, **41**, 4483 (1947).

[110] Starkey and Bremner (to Imperial Chemical Industries Ltd.), British Pat. 605,922 (1948); *C. A.*, **43**, 1064 (1949).

[111] Peters (to The Quaker Oats Co.), U. S. Pat. 2,082,025 (1937); *C. A.*, **31**, 4991 (1937).

[112] Kotake and Fujita, *J. Chem. Soc. Japan*, **51**, 354 (1930); *C. A.*, **25**, 3649 (1931).

[113] Komatsu and Masumoto, *Bull. Chem. Soc. Japan*, **5**, 241 (1930); *C. A.*, **24**, 5718 (1930).

[114] Katuno (to Institute of Fuel Research), Japanese Pat. 153,860 (1942); *C. A.*, **43**, 3464 (1949).

[115] Rapoport and Rapoport, *J. Applied Chem. U. S. S. R.*, **11**, 723 (1938); *C. A.*, **33**, 1660 (1939).

[116] Scott and Johnson, *J. Am. Chem. Soc.*, **54**, 2549 (1932).

[117] Dinelli and Marini-Bettolo, *Gazz. chim. ital.*, **71**, 117 (1941); *C. A.*, **36**, 1928 (1942).

[118] Newth and Wiggins, *Research* (London), **3**, Suppl. 50 (1950); *C. A.*, **44**, 6848 (1950).

copper at 170° and vapor phase, furfural formed 60 per cent furfuryl alcohol and 40 per cent 2-methylfuran.[119] If the temperature was lowered to 140°, no 2-methylfuran was formed, but conversion of furfural was incomplete. An extensive study of the reaction over a number of copper catalysts[15] (see also [119a]) showed that high temperatures ($\leqslant 300°$) or added chromite favored formation of 2-methylfuran, whereas low temperatures ($\geqslant 200°$) or added alkalies favored formation of furfuryl alcohol. By attention to these factors, maximum yields of 89 per cent 2-methylfuran or of 73 per cent furfuryl alcohol were obtained. The comparative rate of hydrogenolysis, acetophenone > furfural >> acetone, was established by Bremner and Keeys.[15] The use of copper-chromite at even lower temperatures (105–146°) allowed yields of about 90 per cent furfuryl alcohol.[120] At higher temperatures, with copper-chromite, other workers[44, 84, 121, 9, 122, 132, 124] have obtained 2-methylfuran as the principal product in yields as high as 95 per cent.

With other copper catalysts, low temperature (130–140°) also favors formation of furfuryl alcohol,[125] while temperatures in the 200° range favor 2-methylfuran in yields as high as 85 per cent.[126, 84, 25, 85] In the light of the above, it is rather surprising to find a patent[127] which claims yields of from 70 per cent to 88 per cent furfuryl alcohol from vapor phase hydrogenation of furfural over copper catalysts with added sodium carbonate at temperatures of 255 to 265°, especially since the patent is issued to the same group who had published the finding[15] that 2-methylfuran is the principal product at the above temperatures.

The hydrogenation of furfural directly to tetrahydrofurfuryl alcohol is best done over Raney nickel because moderate temperatures may be employed in order to minimize hydrogenolysis. Thus, at 90°, an 89 per cent yield of tetrahydrofurfuryl alcohol from furfural was obtained,[128] whereas use of the same catalyst at 210–220° gave a high yield of pentanediols along with some tetrahydrofurfuryl alcohol, 2-methyltetrahydrofuran and

[119] Guinot (to Les Usines de Melle), U. S. Pat. 2,456,187 (1948); *C. A.*, **43**, 2218 (1949).

[119a] Imperial Chemical Industries of Australia & New Zealand, Australian Pat. 135,530 (1949); *C. A.*, **44**, 4932 (1950).

[120] Brown and Hixon, *Ind. Eng. Chem.*, **41**, 1382 (1949).

[121] Johns and Burnette (to Iowa State College Research Foundation), U. S. Pat. 2,458,857 (1949); *C. A.*, **43**, 3465 (1949).

[122] Guenther and Langenau, *J. Am. Chem. Soc.*, **65**, 959 (1943).

[124] Burnette, Johns, Holdren and Hixon, *Ind. Eng. Chem.*, **40**, 502 (1948).

[125] Stichnoth, "Furfuryl Alcohol from Technical Furfural," PB No. **671**, U. S. Dept. Commerce, 1943.

[126] Bremner, Keeys, Jones and Imperial Chemical Industries Ltd., British Pat. 634,079 (1950); *C. A.*, **44**, 6886 (1950).

[127] Jones, Bremner, Keeys and Imperial Chemical Industries Ltd., British Pat. 621,743 (1949); *C. A.*, **43**, 7049 (1949); French Pat. 942,332 (1949).

[128] Hill, *Bull. soc. chim.* (*5*), **4**, 1630 (1937).

tetrahydrofuran.[37, 111] Raney nickel has been used in continuous processes for conversion of furfural to tetrahydrofurfuryl alcohol.[129] Hydrogenation of furfural over Raney nickel in an aqueous acetic acid solution causes extensive hydrogenolysis so that the principal products are pentanediols and pentanetriol.

Nickel-chromite catalysts have been widely used for the reaction of furfural to tetrahydrofurfuryl alcohol at temperatures well below 200°.[130, 131, 132, 133, 134, 135, 136] The effect of temperature on hydrogenolysis can be illustrated as follows[136]:

Reaction products	% Yield	
	150–160°C.	200°C.
Tetrahydrofurfuryl alcohol	95	60
Pentanediols	4	30
Pentyl alcohol	1	10

Similar results have been obtained with other nickel catalysts.[137, 138, 39, 111, 131]

Raney cobalt has been employed in a continuous process in which a mixture of furfural, tetrahydrofurfuryl alcohol and hydrogen was passed over the catalyst at 50° to give a 95 per cent claimed conversion to tetrahydrofurfuryl alcohol.[106, 107] A relatively new catalyst, ruthenium, is said to give a 75 per cent yield of tetrahydrofurfuryl alcohol from furfural.[139] Molybdenum sulfide[140] and molybdenum sulfate[141] have been used for the hydrogenation of furfural. With the sulfide, at less than 230°, 2-methylfuran and pentanol are formed and at 230–320°, 40 per cent 2-methyl-

[129] Starkey and Bremner, British Pat. 608,540 (1948); *C. A.*, **43,** 4700 (1949).

[130] Böhme Fettchemie-Ges. m.b.H., German Pat. 625,477 (1936); *C. A.*, **30,** 2986 (1936).

[131] Rittmeister, U. S. Pat. 2,201,347 (1940); *C. A.*, **34,** 6302 (1940).

[132] Lazier (to E. I. du Pont de Nemours and Co.), U. S. Pats. 2,077,421–2 (1937); *C. A.*, **31,** 3937, 3944 (1937).

[133] Graves (to E. I. du Pont de Nemours and Co.), U. S. Pat. 1,794,453 (1931); *C. A.*, **25,** 2156 (1931).

[134] Natta, Mattei and Bartoletti, Italian Pat. 382,819 (1940); *Chem. Centr.*, **1942,** I, 2930.

[135] E. I. du Pont de Nemours and Co. and Imperial Chemical Industries Ltd., British Pat. 337,296 (1930); *C. A.*, **25,** 1844 (1931).

[136] Deutsche Hydrierwerke A. G., British Pat. 505,600 (1939); *C. A.*, **33,** 7819 (1939).

[137] Schering-Kahlbaum, Akt.-Ges. (Schoeller and Jordan, inventors), German Pat. 555,405 (1930); *C. A.*, **26,** 5102 (1932).

[138] Padoa and Ponti, *Gazz. chim. ital.*, **37,** 105 (1907); *C. A.*, **2,** 1284 (1908).

[139] Howk (to E. I. du Pont de Nemours and Co.), U. S. Pat. 2,487,054 (1949); *C. A.*, **44,** 3029 (1950).

[140] Orlov, *Compt. rend. acad. sci. U. R. S. S.*, **4,** 286 (1934); *C. A.*, **29,** 2905 (1935).

[141] Orlov and Radchenko, *J. Applied Chem. U. S. S. R.*, **9,** 249 (1936); *C. A.*, **30,** 5579 (1936).

furan and mixed hydrocarbons are formed. With the sulfate at 270°, 2-methylfuran, 2-methyltetrahydrofuran and 2-pentanol are produced, while at 330–350°, the products consist of pentane, paraffins, naphthenes and aromatic hydrocarbons.

Platinum catalysts are not useful for the hydrogenation of furfural to tetrahydrofurfuryl alcohol because of the extensive hydrogenolysis encountered.[142, 17, 83, 143] A typical product analysis[142] is:

	%
Tetrahydrofurfuryl alcohol	35
Pentyl alcohol	10
1,2-Pentanediol	20
1,5-Pentanediol	8

Copper catalysts do not, in general, cause hydrogenation of the furan ring of furfural and when the temperature is raised high enough to affect the ring, the major reaction is that of hydrogenolysis. One patent[106] (see also [107]) claims that in a continuous process, furfural and hydrogen passed over Raney copper at as low as 120° formed 30 per cent pentanediols; and at 150°, 30 per cent pentanediols and 30 per cent pentanols were formed. Others[144, 130] claimed an 80–90 per cent yield of tetrahydrofurfuryl alcohol from hydrogenation of furfural over copper at 250°. A more typical experience[24] is the following analysis of products from hydrogenation of furfural over copper-chromite at 250°:

	%
2-Methylfuran	36
Pentanols	36
Furfuryl alcohol + tetrahydrofurfuryl alcohol	13
1,2-Pentanediol	14
1,5-Pentanediol	15
Pentane	0.3

A very extensive survey[145] has been made of the hydrogenation and hydrogenolysis products of furfural over 16 catalysts prepared from nickel, chromium, iron, copper, cobalt and silver in various ratios at temperatures from 180 to 350°. In addition, reaction products from furfural and hydrogen over copper-chromite from 270–350° were studied. In all experiments, extensive hydrogenolysis was observed at the high temperatures employed,

[142] Codignola and Piacenza, Italian Pats. 415,752 (1946) and 417,381 (1947); *C. A.*, **42**, 7101 (1948).

[143] Landrieu, Baylocq and Johnson, *Bull. soc. chim.*, **45**, 36 (1929).

[144] Hachihama and Imoto, *J. Soc. Chem. Ind. Japan*, **45**, Suppl. binding, 19 (1942); *C. A.*, **44**, 8859 (1950); Hachihama, Imoto and Kawata, *Ibid.*, **44**, Suppl. binding, 458 (1941); *C. A.*, **45**, 1573 (1951).

[145] Natta, Rigamonti and Beati, *Chimica e industria Milan*, **23**, 117 (1941); *C. A.*, **35**, 5488 (1941).

but the authors were frustrated in their hope for reaction conditions which would give any one hydrogenolysis product exclusively and in good yield.

5-(Hydroxymethyl)furfural has been hydrogenated over Raney nickel to form tetrahydrofuran-2,5-dimethanol.[118, 146]

In the commercial production of tetrahydrofurfuryl alcohol, the hydrogenation of furfuryl alcohol is preferred to furfural. This may be because, in large scale batches, temperature control is easier to attain when only the heat of hydrogenation of the furan ring must be dissipated. Raney nickel is the preferred catalyst and the yield is inversely related to the temperature at which the reaction can be conducted; high temperatures favor hydrogenolysis.[128, 147, 69] Nickel-on-kieselguhr has also been successfully used for hydrogenation of furfuryl alcohol to tetrahydrofurfuryl alcohol,[47, 102, 103, 109] and yields to 95 per cent have been reported with palladium.[148, 83] Platinum in acetic acid caused complete hydrogenolysis of furfuryl alcohol to 1,2-pentanediol[21] and extensive hydrogenolysis was observed with copper.[109]

Vapor phase hydrogenation of furfuryl alcohol over copper at 170° did not attack the ring but instead, caused complete hydrogenolysis to 2-methylfuran.[119] Copper-chromite catalyzes the reaction of hydrogen with furfuryl alcohol to give mainly hydrogenolysis products. At 175°, pentanediols (70 per cent) predominated in the product,[8] whereas at 250°, pentanols (63 per cent) were formed.[24] At 250°, nickel catalysts caused extensive hydrogenolysis of furfuryl alcohol, and copper-chromite caused almost complete hydrogenolysis.[145]

The furylalkanols present little difficulty in hydrogenation of the ring. Usually nickel, mostly of the Raney type, is used and examples of such hydrogenations are shown in Table 7.

Not only were the phenyl groups unchanged, but with *o*-2-furfurylphenol, the phenolic hydroxyl group was also untouched. The significantly lower yield of those hydrogenations conducted at 150 and 175° is apparent. That the loss is due to hydrogenolysis can be seen from the run with 1-(2-furyl)-1-propanol from which, in addition to the desired 1-(2-tetrahydrofuryl)-1-propanol, there were identified 2-propyltetrahydrofuran, 2-propylfuran, dipropyl ketone and a glycol.[150]

Palladium catalyst has been applied to the hydrogenation of 1-(2-furyl)-

[146] Haworth, Jones and Wiggins, *J. Chem. Soc.*, **1945**, 1.
[147] Paul, *Bull. soc. chim.* (*5*), **4**, 846 (1937).
[148] Wienhaus, *Ber.*, **53**, 1656 (1920).
[149] Duveen, *Compt. rend.*, **206**, 1974 (1938).
[150] Pawlinoff and Wagner, *Ber.*, **17**, 1967 (1884).
[151] Dounce, Wardlow and Connor, *J. Am. Chem. Soc.*, **57**, 2556 (1935).
[152] Normant, *Ann. chim.*, **17**, 335 (1942).
[153] Paul and Normant, *Bull. soc. chim.* (*5*), **5**, 1148 (1938).
[154] Paul and Normant, *Compt. rend.*, **204**, 1482 (1937).

3-butene-1,2-diol and 1-(2-furyl)-3-pentene-1,2-diol with saturation of the ring and double bond to form the respective tetrahydrofurylglycols.[155] Ruthenium catalyst allowed hydrogenation of 2,5-furandipropanol to an 85 per cent yield of 2,5-tetrahydrofurandipropanol.[34] An 80 per cent yield of 1-(2-tetrahydrofuryl)-1-butanol was obtained from hydrogenation of 1-(2-furyl)-1-butanol over platinum, but with 10 per cent of 4,5-octanediol

TABLE 7. HYDROGENATION OF FURYLALKANOLS OVER NICKEL

Compound	Temp. (°C.)	Product (yield)	Ref.
1-(2-Furyl)ethanol	70–80	1-(2-tetrahydrofuryl)ethanol (—)	149
1-(2-Furyl)ethanol	60–80	1-(2-tetrahydrofuryl)ethanol (90%)	147
1-(2-Furyl)-1-propanol	60–80	1-(2-tetrahydrofuryl)-1-propanol (90%)	147
1-(2-Furyl)-1-propanol	175	1-(2-tetrahydrofuryl)-1-propanol (—)	150
1-(2-Furyl)-1-butanol	60–80	1-(2-tetrahydrofuryl)-1-butanol (90%)	147
3-(2-Furyl)-3-pentanol	150	3-(2-tetrahydrofuryl)-3-pentanol (67%)	151
5-(2-Furyl)-5-nonanol	175	5-(2-tetrahydrofuryl)-5-nonanol (58%)	151
1,5-Di(2-furyl)-3-pentanol	—	1,5-di(2-tetrahydrofuryl)-3-pentanol (70%)	51
(2-Furyl)phenylcarbinol	70–80	(2-tetrahydrofuryl)phenylcarbinol (90%)	147, 52
o-2-Furfurylphenol	110	*o*-2-tetrahydrofurfurylphenol (—)	152, 153, 154

as a by-product due to hydrogenolysis.[156] Molybdenum sulfide caused hydrogenation of 1-(2-furyl)-1-propanol at 240° to produce a 30–35 per cent yield of heptane[157] and a similar yield at 300–315°.[140]

Very few furan ethers have been hydrogenated. Three of these possessed benzene rings and were hydrogenated smoothly over Raney nickel. Only the furan ring was reduced:

Phenyl furfuryl ether[153, 154]
o-2-Furylanisole[152, 153]
o-2-Furyl-*p*-methylanisole[152]

[155] Wiemann, *Bull. soc. chim.* (*5*), **2**, 1209 (1935).
[156] Kondo and Takeda, *J. Pharm. Soc. Japan*, **55**, 734 (1935); *C. A.*, **29**, 7324 (1935).
[157] Orlov, Glinskikh and Ignatovich, *J. Applied Chem. U. S. S. R.*, **8**, 1170 (1935); *C. A.*, **30**, 5555 (1936).

Platinum catalyzed the hydrogenation of 2,2′-methylenedi(3-furylmethyl) ether to the 2-2′-methylenedi(3-tetrahydrofurylmethyl) ether.[158]

Other Furan Aldehydes

The hydrogenation of furylacrolein and related types (Table 8) may involve selective hydrogenation of the aldehyde, ethylene and furan ring, as well as hydrogenolysis and of cyclization to 1,9-dioxa-5-spirononanes. Factors effecting formation of the latter have been discussed (p. 685).

It is evident that with nickel, the ethylene bond is attacked before the aldehyde group, and that the higher temperatures are required for hydrogenation of the furan ring. With platinum, hydrogenation of the aldehyde took place selectively when zinc was used as a selective poison. Without the zinc, the usual course of hydrogenation was observed.

Ketones

The hydrogenation of furylalkanones and furylalkenones, such as are prepared by condensation of furfural and a ketone, has been studied extensively. The usual problems of selective hydrogenation, hydrogenolysis and cyclization are encountered. The results, shown in Table 9, are generally arranged according to the ketone used to prepare the starting furylalkenones.

Hydrogenation of furoin led to the diastereoisomeric 1,2-di(2-tetrahydrofuryl)-1,2-ethanediols in 93 per cent yield over nickel[47] and 52 per cent yield over platinum.[17] Only the carbonyl group was reduced when 4-(2-furyl)-4-hydroxy-2-butanone hydrogenated over nickel (temperature not specified) to give an 80 per cent yield of 1-(2-furyl)-1,3-butanediol.[160]

In several instances, furan diketones were hydrogenated.[172] 1-(2-Furyl)-

[158] Dinelli and Marini, *Gazz. chim. ital.*, **67**, 417 (1937); *C. A.*, **32**, 1261 (1938).
[159] Hofmann, Chen, Bridgwater and Axelrod, *J. Am. Chem. Soc.*, **69**, 191 (1947).
[160] Schmauss and Haberland, "Furfural Condensation," PB No. **739**, U. S. Dept. Commerce, 1943.
[161] Gilman and Hewlett, *Rec. trav. chim.*, **51**, 93 (1932).
[162] Kleene, *J. Am. Chem. Soc.*, **63**, 3539 (1941).
[163] Gilman and Dickey, *J. Am. Chem. Soc.*, **52**, 2144 (1930).
[164] I. G. Farbenindustrie, "Work in the Furfural Field," PB No. **804**, U. S. Dept. Commerce, 1941.
[165] German Pat. 476,189 (1937); *Chem. Centr.*, **1938, I**, 3535.
[166] Zerweck, "Furfural as a Starting Material for New Solvents and Plasticizers," PB No. **42436**, U. S. Dept. Commerce, 1940.
[167] I. G. Farbenindustrie Akt.-Ges., British Pat. 476,189 (1937); *C. A.*, **32**, 3857 (1938).
[168] Alexander (to the United States of America, as represented by the Secy. of Agr.), U. S. Pat. 2,532,279 (1950); *C. A.*, **45**, 3423 (1951).
[169] Alexander and Smith, *J. Am. Chem. Soc.*, **71**, 735 (1949).
[170] Bargellini and Martegiani, *Gazz. chim. ital.*, **42, II**, 427 (1912).
[171] Cornubert, Delmas, Monteil and Viriot, *Bull. soc. chim. France*, **1950**, 36.
[172] Sprague and Adkins, *J. Am. Chem. Soc.*, **56**, 2669 (1934).

1,3-butanedione over Raney nickel gave a 73 per cent yield of 1-(2-tetrahydrofuryl)-1,3-butanediol, but with same catalyst, time and temperature, 1-(2-furyl)-3-phenyl-1,3-propanedione gave only a 30 per cent yield of 1-(2-tetrahydrofuryl)-3-phenyl-1,3-propanediol. Extensive hydrogenolysis accounted for the remainder. Benzyl alcohol and 28 per cent of 1-(2-tetrahydrofuryl)-3-phenyl-1-propanol were identified in the reaction products. Platinum catalyzed the hydrogenolysis of 2,5-bis(3-oxobutyl)furan to a 20 per cent yield of 2,5,11-dodecanetriol,[29] while ruthenium allowed hydrogenation to occur with an 85 per cent yield of 2,5-bis(3-hydroxybutyl)-tetrahydrofuran.[34]

Acids and Their Derivatives

Selective hydrogenation of the ring of furoic acid is readily attained, but not without a serious amount of hydrogenolysis. For instance, over platinum, only a 40 per cent yield of tetrahydrofuroic acid was obtained, the remainder being hydrogenolysis products.[17] The extent of hydrogenolysis is even more pronounced when an acidic solvent is used. Thus 90 per cent of δ-valerolactone and only 10 per cent of tetrahydrofuroic acid were obtained from hydrogenation of furoic acid in acetic acid over platinum.[21] Less hydrogenolysis was observed over a nickel[69] or a palladium catalyst.[173]

Hydrogenation of a furoic salt, such as ammonium furoate[53] (60 per cent yield) or sodium furoate[63, 64] (89 per cent yield) over nickel, does not completely avoid hydrogenolysis.

Other furan acids or salts present a similar problem. Sodium 3-(2-furyl)-acrylate, hydrogenated over nickel gave 64 per cent of 3-(2-tetrahydrofuryl)propionic acid and 10 per cent of heptanoic γ-lactone[63]; but over palladium, only the expected 3-(2-tetrahydrofuryl)propionic acid was obtained.[174] The latter compound was also formed on hydrogenation of sodium 3-(2-furyl)propionate over palladium.[175] 3-(2-Furyl)allylidenemalonic acid has been hydrogenated over palladium, with concomitant decarboxylation, to 5-(2-furyl)valeric acid in a 50 per cent yield.[176]

When free 3-(2-furyl)acrylic acid was hydrogenated over platinum, only a 40 per cent yield of 3-(2-tetrahydrofuryl)propionic acid was reported.[17] The remainder were presumably hydrogenolysis products, such as heptanoic γ-lactone and 4-heptanoic acid.[177] Platinum also caused hydrogenolysis of 2,5-furandipropionic acid, so that in addition to the desired tetrahydro

[173] Wienhaus and Sorge, *Ber.*, **46**, 1927 (1913); *Chem. Centr.*, **1913**, II, 511.

[174] Windaus and Dalmer, *Ber.*, **53**, 2304 (1920).

[175] Sherlin, Berlin, Serebrennikova and Rabinovich, *J. Gen. Chem. U. S. S. R.*, **8**, 7 (1938); *C. A.*, **32**, 5397 (1938).

[176] Hofmann, *J. Am. Chem. Soc.*, **66**, 51 (1944).

[177] Keimatsu, Kato and Fukushima, *J. Pharm. Soc. Japan*, **50**, 653 (1930); *C. A.*, **24**, 5022 (1930).

TABLE 8. HYDROGENATION OF FURYLACROLEIN TYPES

Starting compound	Catalyst	Temp. (°C.)	Products (yield) A = 3-(2-furyl)-1-propanol B = 3-(2-tetrahydrofuryl)-1-propanol C = 1,9-dioxa-5-spirononane	Ref.
3-(2-Furyl)acrolein	Ni(R)	23	3-(2-furyl)propionaldehyde (46%) A (—)	47
3-(2-Furyl)acrolein	Ni(R)	25	A (80%)	159
3-(2-Furyl)acrolein	Ni(R)	175–180	B (75%) C (12%) 1,4,7-heptanetriol	18, 49
3-(2-Furyl)acrolein	Ni(R)	160	B (65%) C (3%)	47
2-Ethyl-3-(2-furyl)acrolein	Ni(R)	175	2-ethyl-B (81%) 3-ethyl-C (10%)	18
3-(2-Furyl)acrolein	Ni	160	B (38%) C (38%) 2-ethyltetrahydrofuran (3%)	47
3-(2-Furyl)acrolein	Ni	80	3-(2-furyl)propionaldehyde (—)	62
3-(2-Furyl)-2-(tetrahydrofurfuryloxy-methyl)acrolein	Ni	170	3-(2-tetrahydrofuryl)-2-(2-tetrahydrofurfuroxy-methyl)-1-propanol (50%) 3-methyl-C (30%)	50
3-(2-Furyl)-2-(methoxymethyl)acrolein	Ni	140	3-(2-tetrahydrofuryl)-2-(methoxymethyl)pro-panol (47%) 3-methyl-C (50%)	50
3-(2-Furyl)propionaldehyde	Ni	160	B (29%) C (28%)	47
3-Hydroxy-3-(2-furyl)propionaldehyde	Ni	—	1-(2-furyl)-1,3-propanediol (80%)	160
5-(2-Furyl)penta-2,4-dienal	Ni(R)	170	5-(2-tetrahydrofuryl)-1-pentanol (96%)	18, 49
3-(2-Furyl)acrolein	Ca-chromite	120–175	A (72%) C (4%)	47

3-(2-Furyl)acrolein	Ca-chromite	200	B (22%) 1,4-heptanediol (29%) 1,7-heptanediol (20%) *n*-heptanol (4%)	47
2,5-Furandipropionaldehyde	Ca-chromite	145–175	2,5-furandipropanol (80%)	34
2,5-Furandipropionaldehyde	Ru	100	2,5-tetrahydrofurandipropanol (85%)	34
3-(2-Furyl)acrolein	Pt + Zn	25	3-(2-furyl)propenol (75%)	4
3-(2-Furyl)acrolein	Pt	25	A (50%) 3-(2-tetrahydrofuryl)propenol(?) (10%) (see p. 689	4
3-(2-Furyl)acrolein	Pt	25	A (55%)	161
3-(2-Furyl)acrolein	Pt	25	B (60%) 1,4-heptanediol (19%)	4, 161
3-(2-Furyl)acrolein	MoS_2	200–250	heptane (12%)	157
3-(2-Furfurylidene)-5-formyldihydropyran	Ni	180	3-(2-tetrahydrofurfuryl)-5-hydroxymethyltetrahydropyran (63%)	50

TABLE 9. HYDROGENATION OF FURYLALKANONES AND FURYLALKENONES

Starting compound	Catalyst	Temp. (°C.)	Products (yield)	Ref.
Furfurylideneacetone	Ni(R)	180	4-(2-tetrahydrofuryl)-2-butanol (77%) 2-methyl-1,9-dioxa-5-spirononane (—)	18
Furfurylideneacetone	Ni	100	4-(2-tetrahydrofuryl)-2-butanol (—)	39
Furfurylideneacetone	Ni	125	4-(2-tetrahydrofuryl)-2-butanol (63%)	162
Furfurylideneacetone	Ni	150	4-(2-tetrahydrofuryl)-2-butanol (89%)	47
1-(2-Furyl)-2-butanone	Ni(R)	125	1-(2-tetrahydrofuryl)-2-butanol (83%)	31
Furfurylideneacetone	Cu-chromite	110–135	4-(2-furyl)-2-butanol (85%) 2-methyl-1,9-dioxa-spirononane (10%)	51
Furfurylideneacetone	Pt	25	4-(2-tetrahydrofuryl)-2-butanone (25%)	163
Furfurylideneacetone	Pt	25	4-(2-tetrahydrofuryl)-2-butanone (80%)	17
5-Methylfurfurylideneacetone	Pd	25	4-(5-methyl-2-furyl)-2-butanone (—)	29
4-(5-Methyl-2-furyl)-2-butanone	Pt	25	2,5-nonanedione (—) 2,8-nonanedione (—)	29
2-Furylvinyl isobutyl ketone	Ni	140–150	tetrahydrofurylethyl isobutyl ketone (?; could not prepare semicarbazone) (—)	62
2-Furylacetone	Ni(R)	125	1-(2-tetrahydrofuryl)-2-propanol (55%)	31
1-(2-Furyl)-2-pentanone	Ni(R)	125	1-(2-tetrahydrofuryl)-2-pentanone (80%)	31
Difurfurylideneacetone	Ni	25	1,5-di(2-furyl)-3-pentanone (—)	164
Difurfurylideneacetone	Ni(R) + $CHCl_3$	—	1,5-di(2-furyl)-3-pentanone (—)	5
Difurfurylideneacetone	Ni	25	1,5-di(2-furyl)-3-pentanone (—)	40
Difurfurylideneacetone	Ni + NaOH	25	1,5-di(2-furyl)pentane (—)	40
Difurfurylideneacetone	Ni(R)	—	1,5-di(2-tetrahydrofuryl)pentane (—)	5
Difurfurylideneacetone	Ni	160	1,5-di(2-tetrahydrofuryl)-3-pentanol (90%)	165, 166
Difurfurylideneacetone	Ni	150	1,5-di(2-tetrahydrofuryl)-3-pentanol (—)	164
Difurfurylideneacetone	Ni	140–150	1,5-di(2-tetrahydrofuryl)-3-pentanol (—) 1-(2-tetrahydrofuryl)-3-butanol (—)	167
Difurfurylideneacetone	Ni	150	1,5-di(2-furyl)-3-pentanone (—)	166
Difurfurylideneacetone	Cu-chromite	110–135	1,5-di(2-furyl)-3-pentanone (70%) 1-(2-furylethyl)-1,9-dioxa-5-spirononane (15–25%)	51

Difurfurylideneacetone	Cu-chromite	170–180	C_{13} triols (—)	164
1,5-Di(2-furyl)-2-methyl-1,4-pentadien-3-one	Cu-chromite	110–135	2-methyl-1,5-di(2-furyl)-3-pentanol (55%)	51
6-(2-Furyl)-3,5-hexadien-2-one	Ni(R)	175	6-(2-tetrahydrofuryl)-2-hexanol (84%)	18
6-(2-Furyl)-3,5-hexadien-2-one	Ni	100	6-(2-furyl)-2-hexanone (—)	62
1,9-Di(2-furyl)-1,3,6,8-nonatetraen-5-one	Ni(R)	175	1,9-di(2-tetrahydrofuryl)-5-nonanol (81%)	18, 49
1,9-Di(2-furyl)-1,3,6,8-nonatetraen-5-one	Cu-chromite	110–135	1,9-di(2-furyl)-5-nonanol (50%)	51
Furfurylideneacetophenone	Ni	70	ω-furfurylacetophenone (80%)	157
Furfurylideneacetophenone	Ni	135	3-(2-tetrahydrofuryl)-1-phenyl-1-propanol (25%) 1-(2-tetrahydrofuryl)-3-phenylpropane (31%)	47
Furfurylideneacetophenone	Pt	25	ω-tetrahydrofurfurylacetophenone (70%)	17
Furfurylideneacetophenone	Pt	25	3-(2-tetrahydrofuryl)-1-phenyl-1-propanol (85%)	17
ω-(5-Methylfurfurylidene)acetophenone	Pd	25	ω-(5-methylfurfuryl)acetophenone (—)	29
2-Furyl styryl ketone	Cu-chromite	110–135	1-(2-furyl)-3-phenyl-1-propanol (93%)	51
2-Furyl β-(2-furyl)vinyl ketone	Ni(R)	130–150	1,3-di(2-tetrahydrofuryl)-1-propanol (95%)	168
2-Furyl β-(2-furyl)vinyl ketone	Ni(R)	130	1,3-di(2-tetrahydrofuryl)-1-propanol (—)	168, 169
2-Furyl β-(2-furyl)vinyl ketone	Ni	40–50	2-furyl furfurylmethyl ketone (85%)	168
2-Furyl β-(2-furyl)vinyl ketone	Ni	45–65	2-furyl furfurylmethyl ketone (95%)	168, 169
2-Furyl β-(2-furyl)vinyl ketone	Cu-chromite	90–115	1,3-di(2-furyl)-1-propanol (90%)	168, 169
1,5-Di(2-furyl)-2,4-pentadien-1-one	Cu-chromite	110–135	1,5-di(2-furyl)-1-pentanol (95%)	51
2,5-Difurfurylidenecyclopentanone	Cu-chromite	110–135	2,5-difurfurylcyclopentanol (80%)	51
2,6-Difurfurylidenecyclohexanone	Cu-chromite	110–135	2,6-difurfurylcyclohexanol (55%)	51
2-(3-(2-Furyl)acrylyl)pyrrole	Pd	100	2-(3-(2-furyl)propionyl)pyrrole (—)	170
3,5-Difurfurylidenetetrahydro-4-pyranone	Ni	65	3,5-difurfuryltetrahydro-4-pyranone (30%)	171

acid, sebacic acid was isolated.[178] The combined use of nickel and a sodium salt allowed a fair yield (80 per cent) of tetrahydrofurfurylmalonic acid from hydrogenation of sodium furfurylidenemalonate,[63] and of 2-tetrahydrofurylglycollic acid from sodium 2-furylglycollate.[179]

If the esters instead of the free acid or salt are used, hydrogenolysis ceases to be troublesome. Thus, methyl furoate[53] and ethyl furoate[151, 63, 180] have been hydrogenated over Raney nickel, in over 90 per cent yields, to methyl or ethyl tetrahydrofuroate. Even with platinum, an 80 per cent yield of ethyl tetrahydrofuroate was obtained from ethyl furoate.[17] Ethyl 5-(hydroxymethyl)furoate was hydrogenated in 70 per cent yield over nickel to ethyl 5-(hydroxymethyl)tetrahydrofuroate.[146]

Methyl 3-(2-furyl)propionate over platinum gave a poorer yield (50 per cent) of methyl 3-(2-tetrahydrofuryl)propionate than did the ethyl ester (92 per cent) over Raney nickel. Hydrogenation of the β-lactone, 3-(2-furyl)-3-propionolactone, over Raney nickel, gave rise to 3-(2-tetrahydrofuryl)propionic acid in 38 per cent yield.[181] The low yield is not surprising since selective hydrogenolysis of the lactone group is necessary for formation of the product.

A number of workers[47, 180, 63, 64, 18, 182] have hydrogenated ethyl 3-(2-furyl)acrylate over Raney nickel obtaining ethyl 3-(2-tetrahydrofuryl)propionate in approximately 90 per cent yield. Here the ethylene bond as well as the furan ring has been hydrogenated. Equally good yields of the saturated esters have been obtained from hydrogenation over Raney nickel of ethyl furfurylidenemalonate,[18, 63] ethyl furfurylideneacetoacetate,[63] ethyl 4-furfurylidenecrotonate[18] and of ethyl 4-(furfurylidenemethyl)nicotinate.[183]

Acid chlorides in the furan series have been hydrogenated to aldehydes in typical Rosenmund reductions. This has been useful for preparation of 3-furaldehyde from 3-furoyl chloride,[184, 185] 4-methyl-3-furaldehyde from 4-methyl-3-furoyl chloride[186] and of 4-carbomethoxyfurfural from 4-carbomethoxy-2-furoyl chloride.[187]

Due to interest in the following in the synthesis of oxybiotin (see p. 191), a number of 2-substituted-3,4-furandicarboxylic acids, as such or after

[178] Asahina and Fujita, *J. Pharm. Soc. Japan*, **70**, 1, 331 (1921); *Chem. Centr.*, **1921**, III, 484; *C. A.*, **15**, 2439 (1921).

[179] Normant, *Compt. rend.*, **225**, 580 (1947).

[180] Paul, *Bull. soc. chim.*, **8**, 369 (1941).

[181] Hagemeyer (to Eastman Kodak Co.), U. S. Pat. 2,484,499 (1949).

[182] Papa, Schwenk and Ginsberg, *J. Org. Chem.*, **16**, 253 (1951).

[183] Beer and Preobrazhenskii, *J. Gen. Chem. U. S. S. R.*, **16**, 858 (1946); *C. A.*, **41**, 122 (1947).

[184] Hayes, *J. Am. Chem. Soc.*, **71**, 2581 (1949).

[185] Gilman and Burtner, *J. Am. Chem. Soc.*, **55**, 2903 (1933).

[186] Reichstein and Grüssner, *Helv. Chim. Acta*, **16**, 28 (1933).

[187] Gilman, Burtner and Smith, *J. Am. Chem. Soc.*, **55**, 403 (1933).

conversion to esters or urethans, have been hydrogenated to their corresponding tetrahydrofuran derivatives.

Formation and Hydrogenation of Amines

The amide group is sufficiently resistant to reduction so that the ring of a furan amide may be selectively hydrogenated. Furamide has been hydrogenated in good yield over nickel[63] and over palladium[87] to tetrahydrofuroic acid. An example of hydrogenation of the ring, by a copper-chromite catalyst, at high temperature is that in which 2-furopiperidide, at 250°, formed 85 per cent of tetrahydro-2-furopiperidide, along with 3 per cent of tetrahydrofurfuryl alcohol.[188] Yet the same authors[189] claim reduction of furamide to a mixture of furfurylamine and difurfurylamine by use of the same catalyst and temperature. In the latter instances, the amide group was reduced. In another experiment, copper-chromite at lower temperatures (170–180°) caused extensive hydrogenolysis of N-acetyl-1,5-di-(2-furyl)-3-pentanamine to give a complex mixture of C_{13} diols and triols possessing the acetamido group.[164]

Hydrogenation of furfural oxime may be complicated by rearrangement to 2-furamide. Paul[190] showed that the rearrangement took place in ethanol in the presence of Raney nickel in 48 hours at room temperature, or in one hour at reflux. Similar difficulty was experienced in the vapor phase over copper.[191] If conditions sufficiently vigorous to afford rapid hydrogenation are employed, furfurylamine and difurfurylamine may be prepared from furfural oxime[192, 190] over nickel or over palladium.[30, 193] Hydrogenation of the ring requires even more strenuous conditions because of the stabilizing effect of the intermediate amine. Thus, tetrahydrofurfurylamine has been prepared from furfural oxime over palladium (+ acid)[30] and over nickel.[192]

When the possibility for rearrangement is absent, the hydrogenation of furylalkanone oximes to the corresponding amines is straightforward. Hass, Susie and Heider[31] converted the oximes of 1-furyl-2-propanone, 1-furyl-2-butanone and 1-furyl-2-pentanone to the respective primary amines, $C_4H_3O—CH_2—CHR—NH_2$, over Raney nickel at room temperature. The ring was not reduced. When furylacrolein oxime in acetic acid was hy-

[188] Wojcik and Adkins, *J. Am. Chem. Soc.*, **56**, 2419 (1934).
[189] Adkins and Wojcik, *J. Am. Chem. Soc.*, **56**, 247 (1934).
[190] Paul, *Bull. soc. chim.* (5), **4**, 1115, 1121 (1937); *Compt. rend.*, **204**, 363 (1937).
[191] Yamaguchi, *Bull. Chem. Soc. Japan*, **1**, 35 (1926); *C. A.*, **21**, 75 (1927).
[192] McNally, Dickey and Gray (to Eastman Kodak Co.), U. S. Pat. 2,338,655 (1944); *C. A.*, **38**, 3672 (1944).
[193] Williams, *Ber.*, **60**, 2509 (1927).

drogenated over platinum, the ring was reduced with the formation of 3-(2-tetrahydrofuryl)propylamine.[194]

The use of high temperatures, or of acidic media, has been applied to hydrogenation of furanalkylamines, shown in Table 10.

TABLE 10. HYDROGENATION OF FURANALKYLAMINES

Compound	Catalyst	Product (yield)	Ref.
Furfurylamine	Pt (HOAc)	tetrahydrofurfurylamine (60%)	30
Furfurylamine	Pt (HCl)	tetrahydrofurfurylamine (81%)	30
Furfurylamine	Pd (HOAc)	tetrahydrofurfurylamine (60%)	30
Furfurylamine	Pd (no acid)	tetrahydrofurfurylamine (0%)	30
Furfurylamine	Pd	tetrahydrofurfurylamine (—)	193
Furfurylamine	Pt	tetrahydrofurfurylamine (—)	195
Furfurylamine	Ni(R) (215°)	1-(2-tetrahydrofurfuryl)piperidine (43%); piperidine (9%)	181
N-ethyl-(5-methylfurfuryl)-amine	Ni(R)	N-ethyl-(5-methyltetrahydrofurfuryl)amine (90%)	196
2-(2-Furyl)ethylamine	Pt	2-(2-tetrahydrofuryl)ethylamine (—)	197
2-(2-Furyl)ethylammonium-oxalate	Pt	3-hydroxyhexylamine (91%)	198
3-(2-Furyl)propylamine	Pt ($FeCl_3$)	3-(2-tetrahydrofuryl)propylamine (95%)	199
3-(2-Furyl)propylamine	Pt	3-(2-tetrahydrofuryl)propylamine (45%) 2-propylpyrrolidine (17%)	200
3-(2-Furyl)propylamine	Pt (HOAc)	3-(2-tetrahydrofuryl)propylamine (88%)	194
2,5-Furanbispropylamine	Ru	tetrahydrofuran-2,5-bispropylamine (80%)	34
2,5-Furanbispropylamine	Ru	tetrahydrofuran-2,5-bispropylamine (85%)	34
2,5-Furanbis(N-methylpropylamine)	Ru	tetrahydrofuran-2,5-bis(N-methylpropylamine) (85%)	34

The conversion of furfurylamine to 1-(2-tetrahydrofurfuryl)piperidine[181] has been considered as a means of production of pyridines from furfural. This is one instance of ring opening during hydrogenation of furanalkylamines. Others involve the formation of 3-hydroxyhexylamine from 2-

[194] Takamoto and Hirohashi, *J. Pharm. Soc. Japan*, **48**, 446 (1928); *C. A.*, **22**, 3409 (1928).

[195] Keimatsu and Takamoto, *J. Pharm. Soc. Japan*, **544**, 506 (1927); *C. A.*, **21**, 3362 (1927).

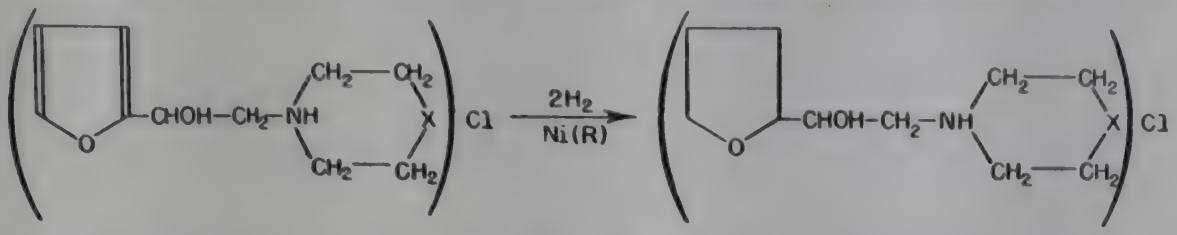
[196] Holdren and Hixon, *J. Am. Chem. Soc.*, **68**, 1198 (1946).

[197] Takamoto, *J. Pharm. Soc. Japan*, **48**, 136 (1928); *C. A.*, **22**, 2354 (1928).

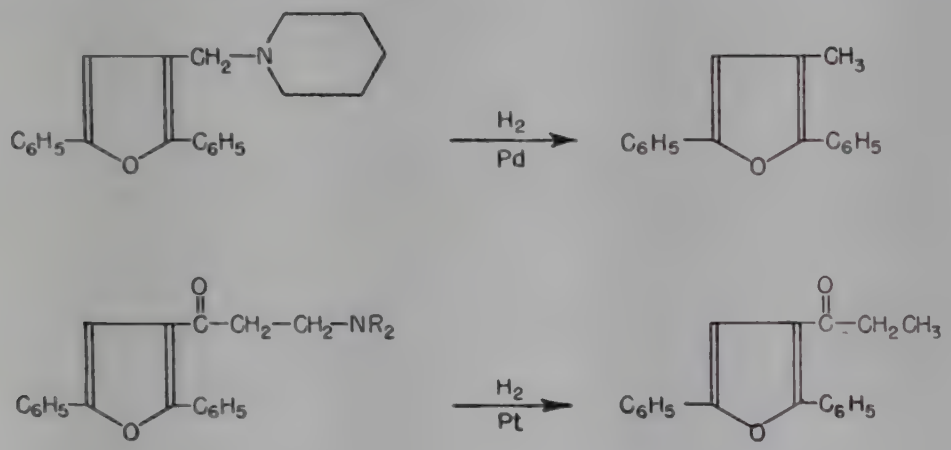
(2-furyl)ethylammonium oxalate[198] and 2-propylpyrrolidine from 3-(2-furyl)propylamine.[200]

Where ferrous chloride has been used with platinum,[199] the action of that chloride may be attributable to its function in producing an acidic medium.

The effect of acidic media on the ease of hydrogenation of furan amines is further apparent in a series of tertiary amine hydrochlorides. In experi-



ments wherein X represented O, CH_2, $CHCH_3$ (from morpholine, piperidine or X-methylpiperidine), 33 to 64 per cent yields of the tetrahydrofuran derivatives were obtained.[33] In another group (the tertiary amines, rather than their salts), the furan ring was untouched, but the amine group was removed by hydrogenolysis.[201, 202]



(R = ethyl or butyl)

On the other hand, if similarly phenylated furan tertiary amines contain halogen atoms, dehalogenation can be achieved by the use of hydrogen and a platinum, palladium or a nickel catalyst, whether the halogen is on a furan or a phenyl ring or on an alkyl side chain. Examples of this are shown in Table 11.

The hydrogenation of furfurin over nickel,[207] is rather interesting in that

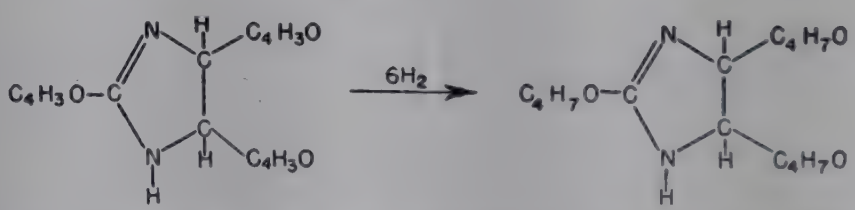
[198] Takamoto, *J. Pharm. Soc. Japan*, **48**, 366 (1928); *C. A.*, **22**, 3162 (1928).
[199] Takamoto, *J. Pharm. Soc. Japan*, **48**, 686 (1928); *C. A.*, **23**, 387 (1929).
[200] Šorm and Brandejs, *Collection Czechoslov. Chem. Communs.*, **12**, 444 (1947); *C. A.*, **43**, 2988 (1949).
[201] Lutz and Rowlett, *J. Am. Chem. Soc.*, **70**, 1359 (1948).
[202] Bailey and Lutz, *J. Am. Chem. Soc.*, **67**, 2232 (1945).
[203] Bailey and Lutz, *J. Am. Chem. Soc.*, **70**, 2412 (1948).

TABLE 11. HYDROGENOLYSIS OF HALOGEN-CONTAINING FURANS
(Pd catalyst)

Starting compound	Product	Ref.
N-(2,5-bis-*p*-bromophenyl-4-bromo-3-furylmethyl)diethylamine	N-(2,5-diphenyl-3-furylmethyl)diethylamine	203
N-(2,5-bis-*p*-bromophenyl-4-bromo-3-furylmethyl)dimethylamine	N-(2,5-diphenyl-3-furylmethyl)dimethylamine	204
N-(2,5-bis-*p*-bromophenyl-4-bromo-3-furylmethyl)morpholine	N-(2,5-diphenyl-3-furylmethyl)morpholine	204
N-(2,5-diphenyl-4-chloro-3-furylmethyl)piperidine*	N-(2,5-diphenyl-3-furylmethyl)piperidine	205
N-(2,5-diphenyl-4-chloro-3-furylmethyl)dimethylamine	N-(2,5-diphenyl-3-furylmethyl)dimethylamine	206
N-(2,5-diphenyl-4-chloro-3-furylmethyl)morpholine	N-(2,5-diphenyl-3-furylmethyl)morpholine	206
3-Bromomethyl-4-chloro-2,5-diphenylfuran	3-methyl-4-chloro-2,5-diphenylfuran	206
3,4-Bis(chloromethyl)-2,5-diphenylfuran†	3,4-dimethyl-2,5-diphenylfuran	206

* Catalyst used, Ni(R).
† Catalyst used, Pt.

while all three furan rings are hydrogenated, the double bond in the imidazole ring is untouched, even at 200°.



Perhaps the relationship of the product to an amidine, stabilized in a 5-membered ring, and sterically hindered by the three tetrahydrofuran rings, accounts for the inertness of the remaining double bond.

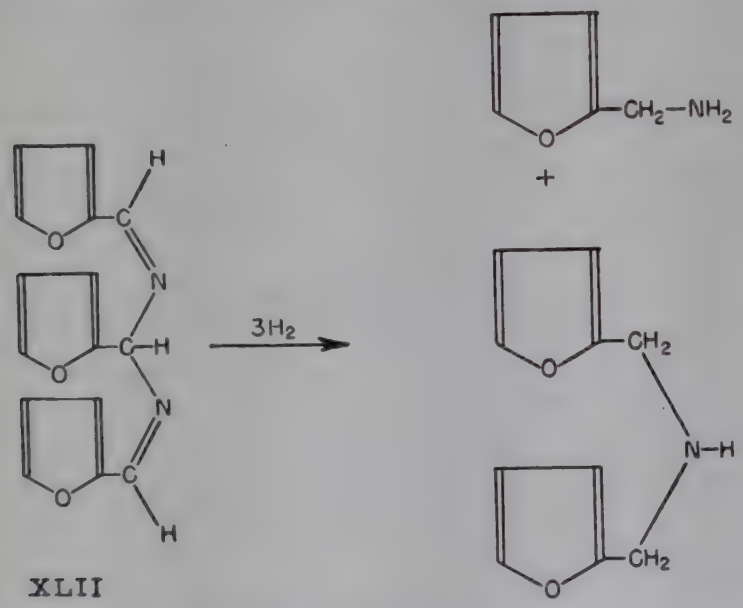
In the preparation of furanalkylamines by reductive amination of a furylalkanone, the severity of conditions determines whether the furanalkylamine, first formed, goes on to form a tetrahydrofuranalkylamine. The problem usually encountered in reductive amination, the effect of the ratio of amine to carbonyl group on the proportions of primary, secondary and tertiary amines formed, is also met in the furan series.[208] For instance, the effect of the ammonia to furfural ratio has been studied, with results shown in Table 12.

[204] Lutz and Bailey, *J. Am. Chem. Soc.*, **67**, 2229 (1945).
[205] Bailey and Nowlin, *J. Am. Chem. Soc.*, **71**, 732 (1949).
[206] Lutz and Bailey, *J. Am. Chem. Soc.*, **68**, 2002 (1946).
[207] Winans and Adkins, *J. Am. Chem. Soc.*, **55**, 2051 (1933).
[208] Huber, *J. Am. Chem. Soc.*, **66**, 876 (1944).

TABLE 12. REDUCTIVE AMINATION OF FURFURAL[209, 210]
(Ni(R), 70°, 90 atm., ethanol medium)

	Products	
	furfurylamine % yield	difurfurylamine % yield
Furfural		
+ 0.50 eq. NH_3	12.2	65.5
+ 0.67 eq. NH_3	30.3	66.5
+ 1.00 eq. NH_3	79	6.0
Hydrofuramide	29.4	62.8
+ excess NH_3	62.5	12.4
+ excess furfural	16.4	60.5

Adkins[207] suggested that the ratio of products obtained from hydrofuramide (XLII), which is equivalent to 0.67 moles NH_3/mole of furfural, is approximately that which would be expected if hydrogenolysis of hydrofuramide took place simultaneously with hydrogenation.



XLII

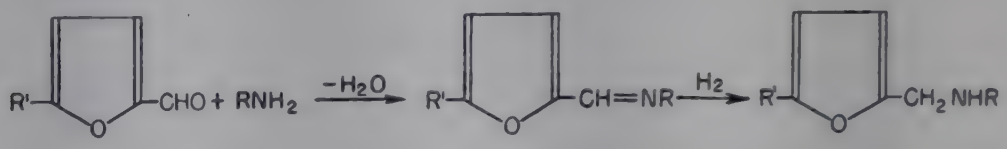
The above also may explain the fact that no tertiary amine has been reported from reductive amination of furfural with a nickel catalyst.[211, 212, 213, 214, 215, 216] The procedure for preparation of furfurylamine from furfural in "Organic Syntheses"[217] calls for liquid ammonia and Raney nickel catalyst. It is interesting to note, however, that in the only reported case

[209] Winans, *J. Am. Chem. Soc.*, **61**, 3566 (1939).
[210] Winans (to Wingfoot Corp.), U. S. Pat. 2,109,159 (1938); *C. A.*, **32**, 2955 (1938).
[211] Schwoegler and Adkins, *J. Am. Chem. Soc.*, **61**, 3499 (1939).
[212] Paul and Tchelitcheff, *Compt. rend.*, **221**, 560 (1945); *Bull. soc. chim.* (5), **12**, 827 (1945).
[213] The Goodyear Tire and Rubber Co., British Pat. 412,914 (1934); *C. A.*, **28**, 7261 (1934).

where a platinum catalyst was employed, a 38 per cent yield of trifurfurylamine was obtained from hydrofuramide.[218]

Other furylalkanones and ammonia also give the primary furanalkylamines with the exception of furfurylideneacetone and ammonia, from which hydrogenation over nickel gave 50 per cent of (1-methyl-3-furylpropyl)amine and 19 per cent of bis(1-methyl-3-furylpropyl)amine.[219]

Hydrogenation of furfural and primary alkyl or aryl amines yields only the secondary amine (XLIV) which might be expected from hydrogenation of a Schiff's base (XLIII).



XLIII XLIV

TABLE 13. FURANALKYLAMINES BY REDUCTIVE AMINATION
(Ni catalysts)

Starting compound	Product (yield)	Ref.
1,5-Di(2-furyl)-3-pentanone + NH_3 (80–100°)	1,5-di(2-furyl)-3-pentanamine (—)	164
1,5-Di(2-furyl)-3-pentanone + NH_3 (180°)	1,5-di-(2-tetrahydrofuryl)-3-pentanamine (—)	164
2,5-Bis(3-oxobutyl)furan + NH_3	2,5-bis(3-aminobutyl)furan (87%)	34
2,5-Bis(3-oxobutyl)furan + CH_3NH_2	2,5-bis(3-methylaminobutyl)furan (85%)	34
2,5-Furandipropionaldehyde + NH_3	2,5-furanbispropylamine (55%)	34
Difurfurylideneacetone + NH_3	1,5-di(2-furyl)-3-pentanamine (—)	166
N-furfurylidenethylamine	N-furfurylethylamine (49%)	225
N-(5-methylfurfurylidene)ethylamine	N-(5-methylfurfuryl)ethylamine (56%)	196
N-furfurylidenebutylamine	N-furfurylbutylamine (75%)	226
N-furfurylideneaniline	N-furfurylaniline (84%)	227
N-furfurylidenebenzylamine	N-furfurylbenzylamine (91%)	226, 228
N-furfurylidene-*p*-hydroxyaniline	N-furfuryl-*p*-hydroxyaniline (99%)	226, 229
N,N′-difurfurylidenebenzidine	N,N′-difurfurylbenzidine (79%)	226
N,N′-difurfurylidene-*p*-phenylenediamine	N,N′-difurfuryl-*p*-phenylenediamine (90%)	226
Furfural + piperidine	N-furfurylpiperidine (90%)	226
2-(Furfurylideneamino)pyridine	2-(2-furfurylamino)pyridine (22%, 75%)	230, 231
2-(5-Bromofurfurylideneamino)pyridine	2-(5-bromo-2-furfurylamino)pyridine (38%)	231
2-(5-Chlorofurfurylideneamino)pyridine	2-(5-chloro-2-furfurylamino)pyridine (62%)	231
N-(3-[2-furyl]allylidene)-*o*-toluidine	N-(3-[tetrahydrofuryl]propyl)-*o*-toluidine (—)	232

Other than the formation of 1-furyl-2-methylamino-1-propanol from hydrogenation of 1-furyl-1-hydroxy-2-propanone and methylamine over platinum,[220] these reactions have all been conducted over nickel and are listed in Table 13.

Catalytic hydrogenation of 2-(*p*-nitrophenyl)furan over Raney nickel gave the expected *p*-2-furylaniline.[221] But hydrogenation of 2-(2-phenyl-2-nitrovinyl)furan over palladium proceeded only to furfuryl phenyl ketoxime[222]; and 2-(*p*-nitrostyryl)furan, over Raney nickel, was hydrogenated only to the azoxy derivative.[223]

A mixture of 84 per cent furfurylamine and 11 per cent difurfurylamine has been obtained from hydrogenation of furonitrile over Raney nickel.[208] When 3-(2-furoyl)propionitrile was similarly treated, the keto amine cyclized to 2-(2-furyl)-2,3-pyrroline.[224]

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[214] Sly (to E. I. du Pont de Nemours and Co.) U. S. Pat. 2,112,715 (1938); *C. A.*, **32,** 3767 (1938).

[215] Adkins and Winans, U. S. Pat. 2,045,574 (1936); *C. A.*, **30,** 5589 (1936).

[216] Cramer (to Wingfoot Corp.), U. S. Pat. 2,047,926 (1936); *C. A.*, **30,** 6008 (1936).

[217] Robinson and Snyder, "Organic Syntheses," Vol. 23, p. 68, New York, John Wiley & Sons, Inc., (1943).

[218] Gilman and Dickey, *Iowa State Coll. J. Sci.*, **5,** 193 (1931).

[219] Haskelberg, *J. Am. Chem. Soc.*, **70,** 2811 (1948).

[220] Knoll A.-G. chem. Fab., Hildebrandt and Klavehn, Ger. Pat. 585,667 (1933); *C. A.*, **28,** 1355 (1934).

[221] Johnson, *J. Chem. Soc.*, **1946,** 895.

[222] Reichert and Kuhn, *Ber.*, **74,** 328 (1941).

[223] Brown and Kon, *J. Chem. Soc.*, **1948,** 2147.

[224] Knott, *J. Chem. Soc.*, **1948,** 186.

[225] Lutz *et al.*, *J. Org. Chem.*, **12,** 760 (1947).

[226] Adkins and Winans, U. S. Pat. 2,175,585 (1939); *C. A.*, **34,** 779 (1940).

[227] Eliel and Peckham, *J. Am. Chem. Soc.*, **72,** 1209 (1950).

[228] Campbell, Ackerman and Campbell, *J. Am. Chem. Soc.*, **71,** 2905 (1949).

[229] Winans, British Pat. 497,778 (1938); *C. A.*, **33,** 4078 (1939).

[230] Lincoln, Heinzelmann and Hunter, *J. Am. Chem. Soc.*, **71,** 2902 (1949).

[231] Hayes, Gever and Orcutt, *J. Am. Chem. Soc.*, **72,** 1205 (1950).

[232] Dickey and McNally (to Eastman Kodak Co.) U. S. Pat. 2,364,350 (1944); *C. A.*, **40,** 2080 (1946).

PART II

INDUSTRIAL APPLICATION OF FURFURAL AND ITS DERIVATIVES

PART II

INTRODUCTION

It is not intended in this section of the monograph to give a detailed account of the multitudinous uses to which furan derivatives have been applied. Rather, an attempt has been made to present a general survey of some of the more important industrial outlets.

Since Dobereiner described the preparation of furfural in 1832, approximately 3500 patents have been issued dealing with furan compounds and their applications. Among these are many which have not attained any industrial importance to date, and others which never developed beyond disclosure. Review articles which include some of these are already available in print,[1, 2, 3, 4, 5, 6] and little will be gained by their inclusion here. In the chapters to follow, the major uses of furfural and its derivatives have been divided into three broad classifications. The treatment given is of a general nature, and it has not been attempted to furnish a complete bibliography. On the other hand, sufficient pertinent references have been cited to assist those interested in obtaining more detailed information.

Prior to a discussion concerned with the utilization of furfural and its derivatives, it seems desirable to give brief consideration to the physiological properties of these compounds. Gilman[7] has observed that "there is nothing inherently offensive physiologically to furan types", and as will be seen (p. 725), many furan compounds possess highly desirable pharmacological properties. In common with other industrial organic compounds, however, the use of furfural and its derivatives is not completely devoid of hazards.

Physiological Properties

Furfural. Practical experience has demonstrated that under ordinary plant conditions the use of furfural is not hazardous to health. In the past fifteen years, many millions of pounds have been employed in solvent refining operations, and in the synthetic resin industry. Occasionally individual sensitivity has been encountered, but other than such allergic mani-

[1] Peters, *Ind. Eng. Chem.*, **28**, 755 (1936); **31**, 178 (1939); **40**, 200 (1948).
[2] Wacek, *Angew. Chem.*, **54**, 453 (1941).
[3] Miner, *Rubber Age*, **19**, 565 (1926).
[4] Trickey and Leuck, *Ind. Eng. Chem.*, **18**, 812 (1926).
[5] Faber, *Seifensieder-Ztg.*, **66**, 534, 554, 574 (1939).
[6] Darling, *Textile Am.*, **37**, 17 (1922).
[7] Gilman, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **6**, 137 (1932).

festations, no injury due to exposure to furfural has been reported. Similarly, in the plants engaged in the production of the aldehyde, no adverse physiological effect has ever been brought to the attention of The Quaker Oats Company other than one, isolated instance of skin irritation and the subject was thereafter, found to be sensitive to aldehydes in general.

Under extreme conditions of exposure to furfural vapors, some pathological effects have been observed on rabbits. Principally, the mucous membranes of the respiratory tract were affected, and the lungs showed marked congestion, particularly in the region of the larger bronchi. On the other hand, these effects were not severe enough to produce death, and it was concluded that the physiological effects of furfural vapors are relatively mild, approximating the same order of magnitude as butyl alcohol.[8] Nevertheless, good ventilation should be provided at all times for the protection of workers, and to minimize discomfort. For example, Korenman and Resnik[9] report that in a factory in Odessa, where the air contained 0.007–0.053 mg. furfural per liter, there was complaint of headaches, itching of the throat, and red, weeping eyes (see also [10]). Additionally, there has been one report that furfural is very damaging to the eyesight of some individuals.[11]

Experiments by McGuigan[12] led to the conclusion that, toward gold fish, furfural is about one-half as toxic as phenol; about one-third as toxic as formaldehyde. A toxicological review[13] summarizes the results of experiments in which furfural was administered to rabbits, dogs and cats by injection or stomach tube. Small doses produced stimulation of the central nervous system, whereas larger doses brought about depression and death due to respiratory paralysis. The fatal dose by mouth is approximately 0.8 ml. per kilogram of body weight. Other references of interest include [14, 15, 16, 17, 18].

In summary, adequate ventilation should be provided where furfural is

[8] Gardner, *Paint and Mfrs. Assoc. of U. S.*, No. **250**, (October, 1925).
[9] Korenman and Resnik, *Arch. Hyg.*, **104**, 344 (1930); *C. A.*, **25**, 2783 (1931).
[10] Kuhn, "Industrial Ophthalmology," C. V. Mosby, St. Louis (1944).
[11] Hamilton, "Recent Changes in the Printers' Trade—Physiological Effect of Solvents," Bull. 7, U. S. Dept. of Labor, Washington, D. C., 1936.
[12] McGuigan, *J. Pharmacol. Exptl. Therap.*, **21**, 65 (1923).
[13] Clinton, "Toxicological Review of Furfural," 3 pp., American Petroleum Institute, New York (March, 1948).
[14] Nakahara and Mori, *Proc. Imp. Acad. Tokyo*, **15**, 278 (1939); *C. A.*, **34**, 1385 (1940); *Gann*, **35**, 208 (1941); *C. A.*, **36**, 2029 (1942).
[15] Hayashi, Kanda, Sato and Matsumiya, *Nagoya J. Med. Sci.*, **6**, 141 (1932); *C. A.*, **27**, 3528 (1933).
[16] Joachimoglu and Klissiunis, *Praktika (Akad. Athenon)*, **7**, 39 (1932); *C. A.*, **28**, 525 (1934).
[17] Cohn, *Arch. exptl. Path. Pharm.*, **31**, 40 (1892).
[18] Lepine, *Compt. rend. soc. biol.*, **39**, 437 (1887).

used. If spilled, it should not be permitted to remain in contact with the skin, since it may act as a local irritant. It is easily enough removed by washing with water. Because of its relatively high boiling point, it is difficult to build up a substantial concentration of furfural in the atmosphere and, generally speaking, its odor is sufficient warning of its presence.

Furfuryl Alcohol. Under normal conditions of handling, neither laboratory nor plant personnel engaged in the manufacture or use of furfuryl alcohol has experienced any impairment of health as a result of exposure to the alcohol. Industrial experience with this compound covers a period of more than fifteen years, and suggests observance of the same general precautions advocated previously for handling furfural.

The physiological action of furfuryl alcohol is reported to be inhibitory and paralytic. Dilute solutions paralyze the sensory nerves.[19] Erdmann[20] reported that 0.6–1.0 grams of furfuryl alcohol (administered as a 5 per cent aqueous solution) caused increased respiration in man; in lesser dosage (40–150 mg.), Joachimoglu and Klissiunis[16] observed no effect on humans.

Unpublished work[21] has revealed that in rats, the $L.D._{50}$ is slightly in excess of 0.1 cc./kg. when the furfuryl alcohol is introduced directly into the stomach. The observed pathological effects included severe hemorrhage and edema of the lungs and congestion of the liver. Regarding the probable effects in man under industrial conditions, it is stated that furfuryl alcohol can be absorbed via the skin, a circumstance which under severe conditions could give rise to haematuria. As a result of this study, several recommendations were made with reference to the use of the alcohol in plant operations. These include 1) precautions to minimize splashing and spraying, 2) immediate washing if the skin is contacted, 3) the use of gloves and goggles where the alcohol is handled in open vessels, and 4) provision for general medical supervision together with periodic urine tests for haematuria. Good plant practice would require that operators immediately remove gloves, shoes or other clothing which has become saturated with the alcohol.

Tetrahydrofurfuryl Alcohol. Toxicological studies on tetrahydrofurfuryl alcohol have been very few in number. Indications from industrial experience, however, strongly suggest that there is little danger to health in normal handling.

Administered by mouth, the minimum lethal dose to rats is in the neighborhood of 6 cc./kg. of body weight. Under conditions of unhindered evaporation, no ill effects were observed when the alcohol was applied to the skin of rats.[22]

[19] Okubo, *J. Pharm. Soc. Japan*, **539**, 39 (1927); *C. A.*, **22**, 4661 (1928).

[20] Erdmann, *Arch. exptl. Path. Pharm.*, **48**, 233 (1902).

[21] Taylor and Frodsham, Imperial Chemical Industries, Ltd., private communication.

[22] The Quaker Oats Company, unpublished work.

As a dye solvent in lipstick preparations, tetrahydrofurfuryl alcohol produces undesirable skin and lip reactions. On the other hand, tetrahydrofurfuryl acetate and other esters show no dermatitic effects under similar conditions.[23]

[23] Gottfried, U. S. Pat. 2,506,921 (1950); *C. A.*, **44**, 8066 (1950).

Chapter 16

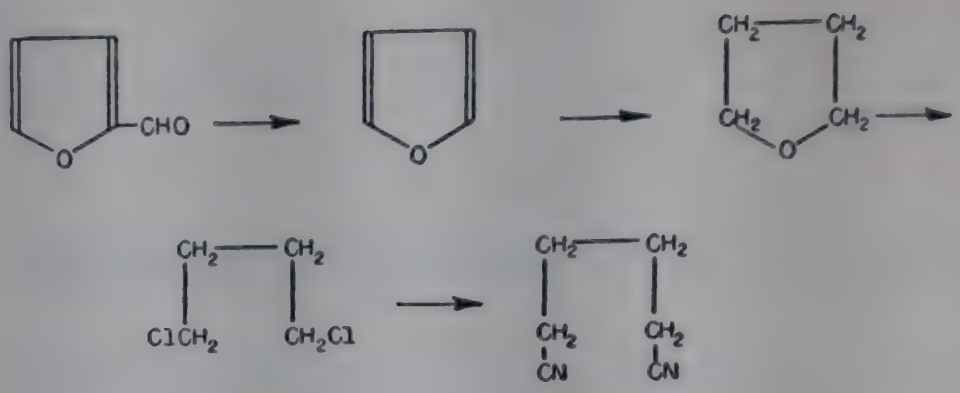
FURFURAL AS A CHEMICAL INTERMEDIATE

At the present time, there is widespread interest in furfural as a raw material for the synthetic organic chemical industry. During the first two decades of commercial availability, its most important applications were largely dependent upon some propitious combination of physical characteristics, as in the several solvent uses (Chapter 17), and the only sizable outlet for furfural as an intermediate was in the production of resins, particularly phenolics (p. 775).

In Part I of this monograph, the chemical properties of the furan family of compounds are discussed in considerable detail. The reader will, therefore, have become cognizant of the great versatility of the furans as a class and of the multiplicity of products which can be derived from furan types, including other heterocyclic compounds and, more important today, difunctional aliphatic and olefinic types. Since furfural is the most economic source of other furan compounds, this suggests that the aldehyde is of great potential value as a chemical intermediate. While this has been recognized by furan chemists for many years, difficulties encountered in obtaining good product yields in syntheses involving furfural and its derivatives have been a deterrent to their industrial utilization as raw materials for other products. As will be seen in the paragraphs to follow, however, such difficulties have been overcome in a number of instances, and the future gives promise of additional developments which will enhance the value of furfural as a chemical intermediate.

Nylon Intermediates

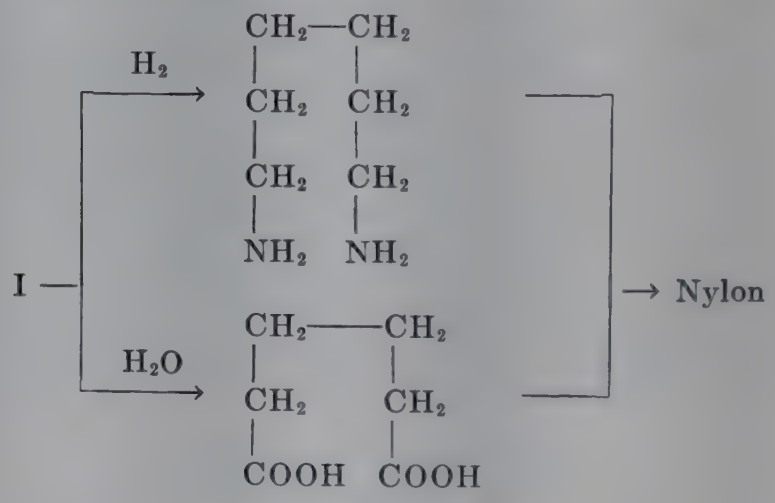
In recent years, wide publicity was given to the announcement, by the du Pont Company, of the development of a process for the manufacture of adiponitrile from furfural. This use as a chemical intermediate is now the largest single outlet for furfural, and the success of the process represents an outstanding industrial achievement. Briefly, it involves four steps as outlined in the following diagram. In the first step, furfural is decarbonylated by passage over a suitable catalyst at elevated temperature



I

(p. 31). The resulting furan is hydrogenated to tetrahydrofuran (p. 690), which is then cleaved by the action of hydrogen chloride[1, 2] to form 1,4-dichlorobutane. Finally, the last is reacted with sodium cyanide under appropriate conditions to obtain adiponitrile, I.

For the production of nylon, two intermediates are required, namely, hexamethylenediamine and adipic acid. While, theoretically, both could be obtained from I, in practice only the former is produced commercially by the furfural process. The first plant for the production of adiponitrile in this manner was erected by the du Pont Company in Niagara Falls, N. Y.,



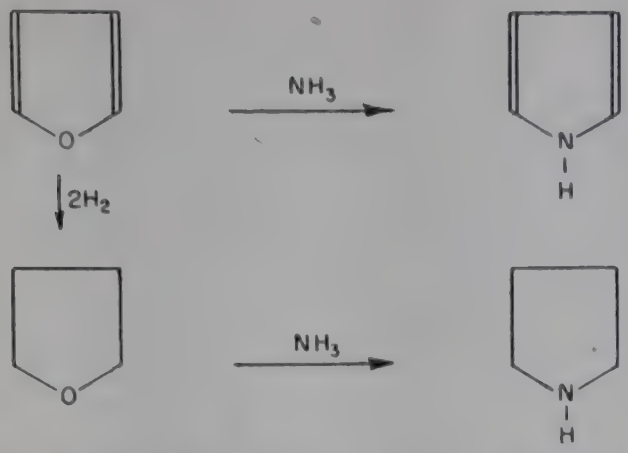
and began operation late in the year 1949. Since then the capacity of this plant has been doubled.

Cass[3] has also announced, for the du Pont Company, the development of processes for the production of pyrrole and pyrrolidine from the first two intermediates in the adiponitrile synthesis, furan and tetrahydrofuran,

[1] Cass, *Ind. Eng. Chem.*, **40**, 216 (1948).

[2] Cass (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,218,018 (1941); *C. A.*, **35**, 1068 (1941).

[3] Cass, *Chemurgic Digest*, **8**, No. 6, 3 pp. (1949).

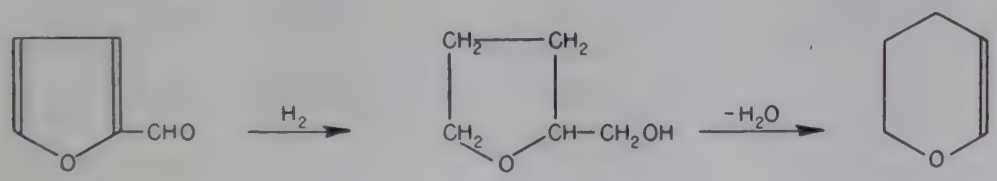


respectively. Thus, for the first time, adequate supplies of pure synthetic pyrrole are available and widespread experimental work is now going on, which, in time, should lead to useful applications. Pyrrolidine has already found use an as intermediate in the synthesis of a series of new drugs.

Aside from chemical intermediate uses, tetrahydrofuran has been found to be an excellent solvent for polyvinyl chloride and polyvinylidene chloride. Clear films can be cast from 10–15 per cent solutions of the former in 65:35 mixtures of tetrahydrofuran and methyl ethyl ketone. Polyvinylidene chloride solutions in tetrahydrofuran are excellent adhesive compositions for sealing plastic bags and sheets.

Dihydropyran and Lysine

Synthesis of the very interesting 2,3-dihydropyran from furfural has been carried out successfully on a practical scale. The furfural is hydrogenated into tetrahydrofurfuryl alcohol (p. 695), which undergoes a rather remarkable dehydration with ring expansion when heated (*ca.* 270°) in contact with a dehydration catalyst such as alumina gel.[1, 4, 5, 6, 7] The product, 2,3-dihydropyran (I), is the basis for a series of new compounds of potential industrial value.



I

One of these compounds, the hydrolysis product, δ-hydroxyvaleraldehyde

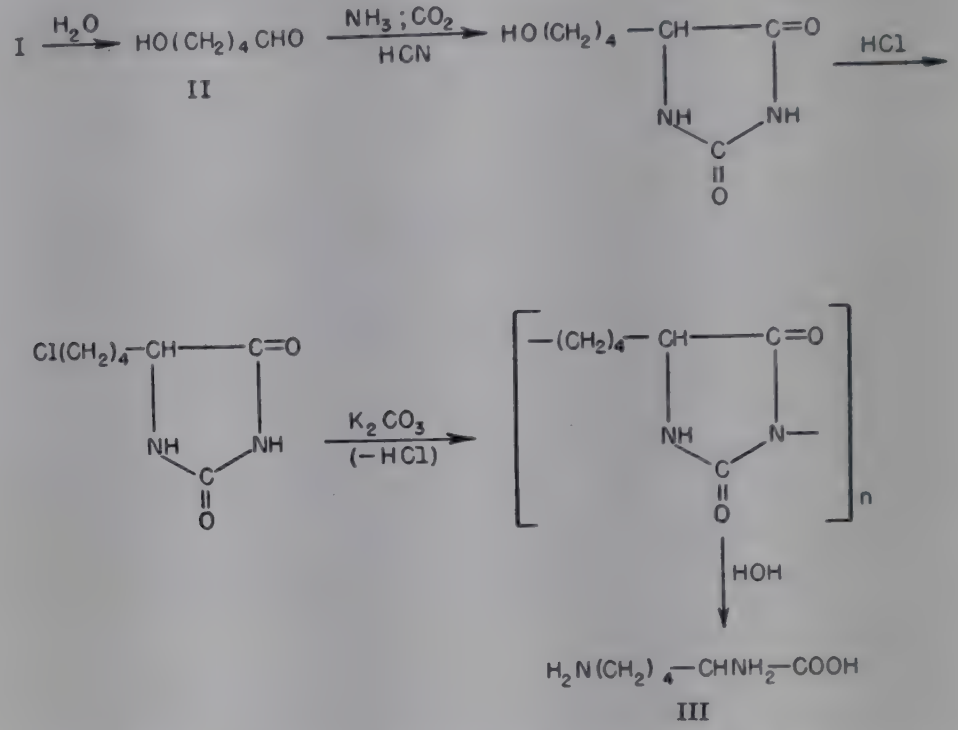
[4] Paul, *Bull. soc. chim.* (*4*), **53**, 1489 (1933).

[5] Sawyer and Andrus, "Organic Syntheses," **23**, 25, New York, John Wiley and Sons, Inc. (1943).

[6] Bremner and McNeil and Imperial Chemical Industries, Ltd., British Pat. 547,334 (1942); *C. A.*, **37**, 5988 (1943).

[7] Revertex Ltd. and Wilson, British Pat. 569,625 (1945); *C. A.*, **41**, 6275 (1947).

(II), offers an economically feasible route to synthetic lysine, III. This complicated synthesis (below) was announced by Rogers *et al.*[8] (see also [9]), in 1948, and full scale development merely awaits sufficient demand for the product. The enrichment of animal feeds, and even human food with synthetic lysine derived from furfural is much more than a remote possibility.



For some of the many other interesting reactions of dihydropyran, primarily those leading to 1,5-difunctional aliphatic compounds (e.g., 1,5-pentanediol, 1,5-dichloropentane, pimelonitrile, glutaric acid, etc.), the reader is referred to the following published work [1, 10, 11, 12].

Furfuryl and Tetrahydrofurfuryl Alcohols and Their Derivatives

The catalytic hydrogenation of furfural over copper chromite is employed on an industrial scale for the production of furfuryl alcohol. The saturated alcohol, tetrahydrofurfuryl alcohol, is similarly produced using Raney nickel catalyst (see p. 695). For the applications of these compounds as solvents and in the resin industry, the reader is referred to Chapters 17 and 18, respectively.

Two sulfur-containing derivatives of furfuryl alcohol have found application in industry. Furfuryl mercaptan, one of the essential constituents of the aroma of roasted coffee, was placed on the market as Coffee-Captan

[8] Rogers *et al.*, Abstracts, Division Organic Chemistry, 114th National Meeting, American Chemical Society, St. Louis, Mo., 1948; *J. Am. Chem. Soc.*, **71**, 1837 (1949).
[9] Gaudry, *Can. J. Res.*, **B, 26,** 387 (1948).
[10] Paul, *Bull. soc. chim.* (*5*), **6,** 1162 (1939).
[11] Schniepp and Geller, *J. Am. Chem. Soc.*, **68,** 1646 (1946).
[12] Andrus, "Organic Syntheses," **23,** 67, New York, John Wiley and Sons, Inc. (1943).

by Cargille Scientific, Inc. during the year 1949. It is reported to offer novel possibilities such as providing a new scent tone for perfumes and serving to enrich flavors and aromas. For a discussion of selected patents on its use as a coffee flavoring agent, see Reichstein and Staudinger.[13] The other sulfur derivative, furfuryl xanthate, was formerly employed in connection with the flotation concentration of ores.[14]

In recent years, furfuryl alcohol has received considerable attention with reference to possible use, in conjunction with nitric acid, as a liquid rocket propellant.[15, 16]

Tetrahydrofurfuryl alcohol finds its greatest market in the synthesis of esters, particularly the oleate, which finds application as a secondary plasticizer for polyvinyl chloride films. Other esters are reported to be of value as plasticizers for cellulose derivatives.[17, 18] Tetrahydrofurfuryl acetate has been used in the United Kingdom as a lipstick ingredient. It is an excellent solvent for eosin and other suitable dyestuffs and is compatible with other lipstick components.

Biological Uses

Included in this classification are the applications of furfural and its derivatives as pharmaceuticals, preservatives, insecticides, fungicides, herbicides and the like.

Pharmaceuticals

Studies relating to the use of derivatives of furfural for the synthesis of pharmaceutical products have led to some important developments. This is particularly true in connection with nitrofuran types, the antibacterial activity of which was discussed in an earlier chapter (p. 164). At the present time, Eaton Laboratories, Inc., manufactures the most powerful of these new disease-fighting drugs, Furacin (5-nitrofurfural semicarbazone), in the form of a solution, and also as a soluble dressing.[19, 20, 21] Most of the current production, however, is being marketed as NFZ (nitrofurazone) for the treatment of coccidiosis, a poultry disease.

[13] Reichstein and Staudinger, *Angew. Chem.*, **62, A,** 292 (1950); *C. A.*, **44,** 8558 (1950).

[14] Keller (to Minerals Separation North American Corp.), U. S. Pat. 1,969,269 (1934); *C. A.*, **28,** 6097 (1934).

[15] Seifert, Mills and Summerfield, *Am. J. Phys.*, **15,** 121 (1947).

[16] Berggren, Ross, Young and Hawk, *J. Am. Rocket Soc.*, **73,** 17 (1948).

[17] Dickey (to Eastman Kodak Co.), U. S. Pat. 2,196,752 (1940); *C. A.*, **34,** 5676 (1940).

[18] Endres (vested in the Alien Property Custodian), U. S. Pat. 2,305,920 (1943); *C. A.*, **37,** 3286 (1943).

[19] Snyder, Kiehn and Christopherson, *Military Surgeon*, **97,** 380 (1945).

[20] Dodd, Hartmann and Ward, *Surg. Gynecol. Obstet.*, **83,** 73 (1946).

[21] Downing, Hanson and Lamb, *J. Am. Med. Assoc.*, **133,** 299 (1947).

Furfuryltrimethylammonium iodide is a parasympathomimetic drug developed by Fellows and Livingston[22] and marketed by Smith, Kline and French Laboratories under the trade name of Furmethide. It may be administered either orally or parenterally, but not intravenously (see p. 248).[23, 24, 25, 26, 27, 28, 29] The antihistaminic activity of derivatives of furfurylamine was mentioned earlier (p. 247).

The antiseptic properties of furfural have been reported[30]; the effectiveness of the aldehyde against *E. typhi* has been discussed by McGuigan.[31] The germicidal activity of furoic acid against *E. coli* and *S. aureus* was mentioned by Kaufmann[32] and later, Calloway[33] reported that several alkylated furoic acids possessed bactericidal properties. For the anti-trypanosome activity of furoic acid, see Ziering and Buck.[34]

As mentioned previously (p. 202), a number of furan mercurials have antiseptic value.[35, 36] Furylmercuric hydroxide has been marketed as an antiseptic solution under the name Furmerane by G. D. Searle and Company.

Derivatives of cinchoninic acid containing the furan ring (analogs of atophan) are, in general, of lower toxicity but also lower activity than atophan (p. 361).[37, 38, 39]

Many other furfural derivatives have been, and are now being studied for use in this general field, and the future should witness interesting and important developments.

Fungicides and Preservatives

In the late 'twenties, sodium 3-(2-furyl)acrylate was exported from the United States to Japan where it was used, in place of cinnamic acid, as a preservative for soya sauce. Manufacture of the product was subsequently transferred to Japan, and still later, the Japanese government prohibited

[22] Fellows and Livingston, *J. Pharmacol. Exptl. Therap.*, **68**, 231 (1940).
[23] Myerson, Rinkel, Loman and Dameshek, *J. Pharmacol. Exptl. Therap.*, **68**, 476 (1940).
[24] Myerson and Thau, *Arch. Ophthalmol.* (Chicago), **24**, 758 (1940).
[25] Uhler, *Am. J. Ophthalmology*, **29**, 447 (1946); **30**, 995 (1947).
[26] Blake, *Am. Profess. Pharmacist*, **11**, 133 (1945).
[27] Lipton, Beaser and Altschule, *Am. J. Med. Sci.*, **206**, 490 (1943).
[28] Lawson and Garvey, *J. Am. Med. Assoc.*, **135**, No. 2, 93 (1947).
[29] Laughlin and Veber, *J. Urology*, **63**, 918 (1950).
[30] Miner, Trickey and Brownlee, *Chem. Met. Eng.*, **27**, 362 (1922).
[31] McGuigan, *J. Pharmacol. Exptl. Therap.*, **21**, 65 (1923).
[32] Kaufmann, *Ber. pharm. Ges.*, **33**, 132 (1923).
[33] Calloway, Gilman and Werkman, *Proc. Iowa Acad. Sci.*, **40**, 81 (1933).
[34] Ziering and Buck, *Jubilee Vol., Emil Barell*, **1946**, 378.
[35] Phatak and Laake, *J. Pharmacol. Exptl. Therap.*, **56**, 265 (1936); **58**, 155 (1936).
[36] Handley, Phatak and Laake, *Univ. Calif., Pub. Pharmacol.*, **1**, 175 (1939).
[37] Mangini, *Ann. chim. applicata*, **27**, 386 (1937); *C. A.*, **32**, 2287 (1938).
[38] Ciusa and Bellino, *Gazz. chim. ital.*, **66**, 452 (1936); *C. A.*, **31**, 3487 (1937).
[39] Ciusa and D'Amato, *Gazz. chim. ital.*, **67**, 776 (1937); *C. A.*, **32**, 4586 (1938).

the use of such preservatives. Since that time, this outlet for furfural has disappeared.

For many years, furfural itself was used as a preservative for starch pastes and glue solutions; embalming fluids for both human beings and biological specimens have been made with furfural.[40, 41, 42, 43] Miner[44] reported its use in aqueous solution for control of wheat smut (*Filletia foetens*); hydrofuramide has been suggested for the same purpose[45] (see also [46]).

Fungus diseases of corn, such as those due to *Diplodia zeae*, *Gibberella saubinetii* (*Mont.*) *Sacc.* or *Basisporium gallarum M. Moll.*, may be controlled by dusting the seed with a fungicide prepared from mercuric chloride and hydrofuramide.[47] For a short period, this product was marketed under the name Sterocide, but has since gone off the market. For related uses, see Reddy.[48, 49] Other references of general interest in the field include Bousquet *et al.*,[50] Melhus.[51, 52]

The new fungicidal ointment, Furaspor, marketed by Eaton Laboratories, Inc., contains 5-nitrofurfuryl methyl ether as the active ingredient. It is especially effective against ringworm of the scalp. When sprayed on sand beaches, furfural destroys fungi, such as the organism which causes "swimmer's itch". As a one per cent solution, it is said to clear up infection by the parasite causing athlete's foot.

For many years, furfural has been used, in conjunction with formaldehyde, as a fumigant for chick incubators. Ready-to-use mixtures for this purpose are being marketed throughout the country with directions as to mode of application and the precautions to observe in order to achieve maximum desired results.

Insecticides

At present, neither furfural itself nor any of its derivatives is in general use as a commercial insecticide. On the other hand, many compounds con-

[40] Miner (to The Quaker Oats Co.), U. S. Pat. 1,554,641 (1925).
[41] McNutt and Bruins, *J. Am. Vet. Med. Assoc.*, **71**, 728 (1927).
[42] Tharaldsen, *Science*, **57**, 305 (1923).
[43] Stowell and Stokes, *J. Technical Methods*, **24**, 25 (1944).
[44] Miner, U. S. Pat. 1,592,039 (1926); *C. A.*, **20**, 3207 (1926).
[45] Trickey and Miner (to The Quaker Oats Co.), U. S. Pat. 1,738,740 (1930); *C. A.*, **24**, 913 (1930).
[46] Borzini and Marini-Bettolo, *Ricerca sci.*, **10**, 878 (1939); *C. A.*, **34**, 4853 (1940).
[47] Reddy (to The Quaker Oats Co.) U. S. Pat. 1,760,000 (1930); *C. A.*, **24**, 3599 (1930).
[48] Reddy, *Phytopathology*, **20**, 147 (1930).
[49] Wilson and Reddy, *Phytopathology*, **21**, 1099 (1931).
[50] Bousquet, Kirby and Searle (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,335,384 (1944); *C. A.*, **38**, 2834 (1944).
[51] Melhus, U. S. Pat. 1,785,641 (1931); *C. A.*, **25**, 554 (1931).
[52] Melhus, *Phytopathology*, **16**, No. 1, 79 (1926).

taining the furan ring have been tested by entomologists, and a number of these have shown considerable promise; a relative of pyrethrum possessing a furan nucleus is now being given active consideration.

For the interested reader, the following partial bibliography is presented:

Baits and repellents: [53, 54, 55, 56, 57, 58, 59, 60]

Insecticides: [61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73]

Herbicides

When mixed with kerosene or light fuel oil, furfural is an effective herbicide, and was so used for several years[74] (see also [75, 76, 77, 78]).

While the above use is no longer active, interest has been shown within

[53] Stellwaag and Götz, *Anz. Schädlingskunde*, **13**, 129 (1937); *C. A.*, **32**, 1847 (1938).

[54] Frost, *J. Econ. Entomol.*, **28**, 366 (1935).

[55] Parman, Bishopp, Laake, Cook and Roark, *U. S. Dept. Agr., Bull. 1472*, "Chemotropic Tests with the Screw Worm Fly," 1927.

[56] Parman, Laake, Bishopp and Roark, *U. S. Dept. Agr., Tech. Bull. 80*, "Tests of Blowfly Baits and Repellents during 1926," 1928.

[57] Bishopp, Roark, Parman and Laake, *J. Econ. Entomol.*, **18**, 776 (1925).

[58] Granett (to National Carbon Co.), U. S. Pat. 2,274,267 (1942); *C. A.*, **36**, 4240 (1942).

[59] Travis, Morton, Jones and Robinson, *J. Econ. Entomol.*, **42**, 686 (1949).

[60] Bartlett and Ross (to U. S. A., as represented by Sec'y of Army), U. S. Pat. 2,564,663 (1951).

[61] Swaine (to General Chemical Co.), U. S. Pat. 2,212,529 (1941); *C. A.*, **35**, 578 (1941).

[62] Siegler, Gertler and Haller, *J. Econ. Entomol.*, **35**, 74 (1942).

[63] Bowen (to the Secretary of Agriculture of the U. S. A. and his successors in office), U. S. Pat. 2,224,243 (1941); *C. A.*, **35**, 1926 (1941).

[64] Swingle, Mayer and Gahan, *J. Econ. Entomol.*, **37**, 672 (1944).

[65] Deonier, Jones and Incho, *J. Econ. Entomol.*, **39**, 459 (1946).

[66] U. S. Dept. Agr., Bureau of Entomology and Plant Quarantine, *Bull. E-733*, "Results of Screening Tests with Materials Evaluated as Insecticides, Miticides and Repellents at the Orlando, Fla., Laboratory, April 1942 to April 1947," September, 1947.

[67] Monsanto Chemical Co., British Pat. 640,570 (1950); *C. A.*, **45**, 8560 (1951).

[68] Gertler and Haller (to the Secretary of Agriculture and his successors in office), U. S. Pat. 2,261,735 (1942); *C. A.*, **36**, 1138 (1942).

[69] Roblin and Hechenbleikner (to American Cyanamid Co.), U. S. Pat. 2,293,309 (1943); *C. A.*, **37**, 1008 (1943).

[70] Eddy and Carson, *J. Econ. Entomol.*, **39**, 763 (1946); **41**, 31 (1948).

[71] Gilman, Heckert, Hewlett and Dickey, *Iowa State Coll. J. Sci.*, **7**, 419 (1933).

[72] Hanson and Cassil (to California Spray-Chemical Corp.), U. S. Pat. 2,406,294 (1946); *C. A.*, **41**, 558 (1947).

[73] Dinelli and Carbotti, *Ann. chim. applicata*, **41**, 391 (1951).

[74] Buckardt, *J. Am. Soc. Agron.*, **28**, 437 (1936).

[75] Thompson and Robbins, *U. S. Dept. Agr., Bull. 1451*, "Methods of Eradicating the Common Barberry," 1926.

[76] Arnold, *Proc. Iowa Acad. Sci.*, **40**, 67 (1933).

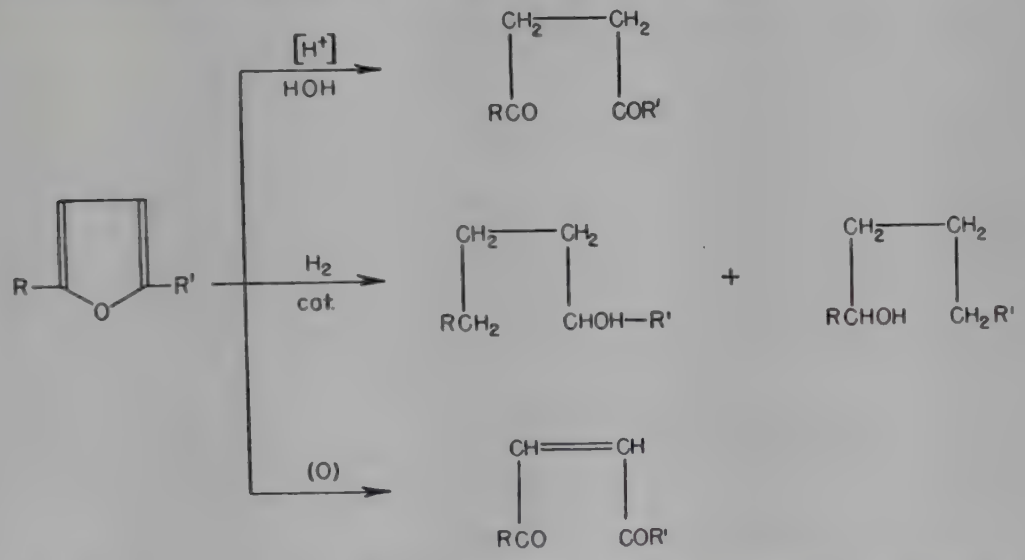
[77] Melhus, U. S. Pat. 2,007,433 (1935); *C. A.*, **29**, 5982 (1935).

[78] Hall (to Tennessee Products Corp.), U. S. Pat. 2,537,995 (1951); *C. A.*, **45**, 3988 (1951).

the past year in the possible use of furan products as cotton defoliants, and for killing narrow-leaved plants. Promising results have been obtained, which may lead to sizable outlets in the future. Recently, for example, tetrahydrofurfuryl esters of 2,4-dichlorophenoxyacetic and 2,4,5-trichlorophenoxyacetic acids have been marketed for use as low volatility brush killers.

Some Potentialities

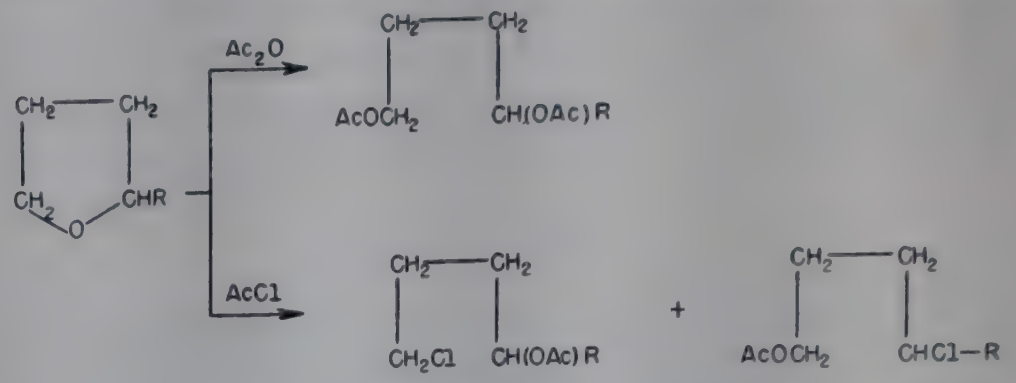
One of the most promising aspects of furan chemistry is concerned with cleavage reactions. Numerous examples of hydrolytic, hydrogenolytic, and oxidative fission of the furan nucleus have been cited throughout Part I of this monograph. To date, however, none of these reactions has attained any degree of industrial significance due, in large measure, to lack of knowledge of the conditions required to promote high product yields. On the other hand, this is likely to be a temporary situation, and might well be overcome should there develop a significant demand for the open-chain compounds obtainable by these various means.



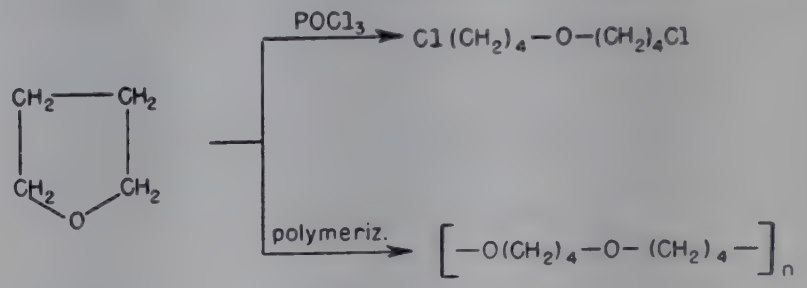
Up to the present time, there has been more industrial interest in the ring opening of saturated furan types. One outstanding example of this has already been discussed in connection with the synthesis of nylon (p. 721). While this represents the most important cleavage reaction of tetrahydrofuran, numerous others have been described. For example, with acetic anhydride under appropriate conditions, it is possible to prepare the diacetate of 1,4-butanediol. The free diol is obtainable by subsequent hydrolysis, other esters by acid interchange. Applied to tetrahydrofurfuryl alcohol, 1,2,5-pentanetriol and its derivatives are formed.[79, 80, 81, 82, 1] The action

[79] Paul, *Bull. soc. chim.* (*4*), **53**, 417 (1933).
[80] Paul, *Bull. soc. chim.* (*5*), **8**, 369 (1941).
[81] Paul, *Bull. soc. chim.* (*5*), **8**, 911 (1941).
[82] Wilson, *J. Chem. Soc.*, **1945**, 48.

of acyl halides cleaves the nucleus to form a halobutyl ester residue,[83, 84, 85]

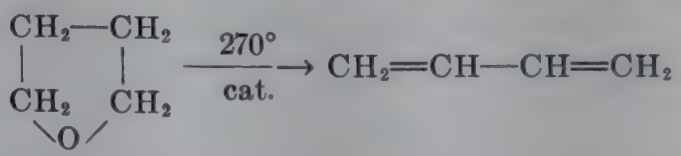


whereas inorganic acid chlorides such as phosphorus oxychloride give rise to 4,4′-dichlorobutyl ether from tetrahydrofuran.[86] Related to the latter



is the work carried on in Germany on the preparation of polymers and copolymers of tetrahydrofuran for use as synthetic lubricants.[87] The catalyst appears as an end group on the polymer chain. Thus, a catalyst system of thionyl chloride and ferric chloride gives a polyether containing chlorine. Copolymers are obtained by incorporating epoxides in the reaction system. Hydroxylated compounds act as chain breakers.

The further importance of tetrahydrofuran to the German chemical industry is attested by estimates indicating that one-fifth of all the butadiene produced in Germany during the war was derived from this source. The process involved dehydration in the vapor phase over a phosphate cata-



lyst.[88, 89] In the same manner, 2-methyltetrahydrofuran gives rise to pi-

[83] Cloke and Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).

[84] Smorgonskiĭ and Gol'dfarb, *J. Gen. Chem. U. S. S. R.*, **10**, 1113 (1940); *C. A.*, **35**, 4011 (1941).

[85] Paul, *Bull. soc. chim.* (5), **5**, 1053 (1938).

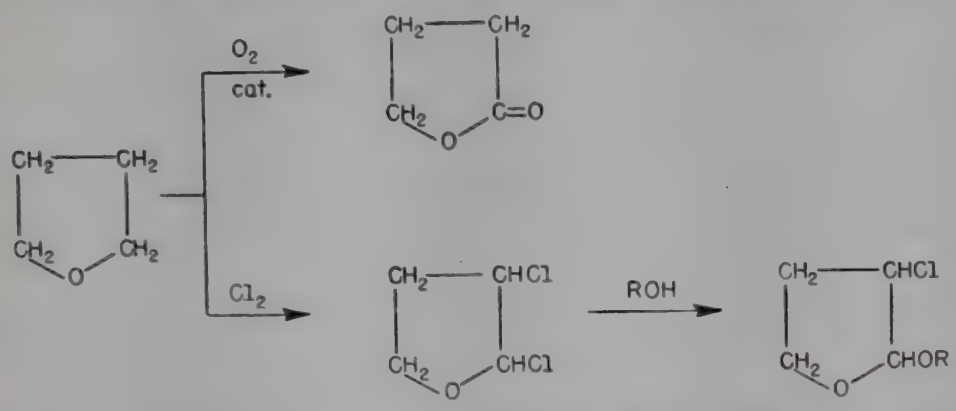
[86] Alexander and Schniepp, *J. Am. Chem. Soc.*, **70**, 1839 (1948).

[87] Delfs, "Polymerization of Tetrahydrofuran," PB No. **717**, U. S. Dept. Commerce, 1941.

[88] Industrial Intelligence Staff, Chemical Warfare Service, *Chem. Eng. News*, **23**, No. 17, 1516 (1945); Hasche, *Chem. Eng. News*, **23**, No. 20, 1840, 1846 (1945).

perylene, 1,3-pentadiene.[90] Neither process has any value in present American economy. Yet another use in Germany involved the production of adipic acid by reaction of tetrahydrofuran with carbon monoxide in the presence of a nickel carbonyl catalyst.[91]

The oxidation of tetrahydrofuran with air or oxygen over a cobalt catalyst gives rise to γ-butyrolactone which was produced in this manner in Germany as an intermediate for the manufacture of the synthetic blood plasma, polyvinylpyrrolidone (Periston). Chlorination of tetrahydrofuran gives primarily, 2,3-dichlorotetrahydrofuran, in which the chlorine atom situated alpha to the nuclear oxygen is very reactive, as indicated below by the formation of a cyclic acetal on reaction with alcohol.[1]



Many more reactions could be cited, but these will serve to illustrate some of the many and varied types of compounds which can be derived from furfural, which in its relatively short industrial history has become an increasingly important intermediate for the chemical industry.

[89] I. G. Farbenindustrie A.-G., British Pat. 506,038 (1939); *C. A.*, **33**, 9328 (1939).

[90] Guinot (to Les Usines de Melle), U. S. Pat. 2,273,484 (1942); *C. A.*, **36**, 4371 (1942).

[91] Paul, *Bull. soc. chim. France*, **1947**, 158, 165.

Chapter 17

SOLVENT APPLICATIONS OF FURFURAL AND ITS DERIVATIVES

The excellent solvent properties of furfural, furfuryl alcohol, tetrahydrofurfuryl alcohol and other furan derivatives have resulted in the development of a variety of industrial uses. In fact, until recently, the largest outlet for furfural itself was based on its unique solubilizing characteristics which, coupled with its ease of recovery by steam distillation (Chapter 8), earned for this aldehyde several large-scale applications. The most notable of these are the purification of wood rosin, the refining of lubricating oils, and the separation of butadiene in high purity from mixtures of C_4 hydrocarbons. All three are dependent upon the differential solvation of the several components of complex mixtures. The first two involve selective solvent extraction procedures, while the third is accomplished by the extractive-distillation technique. The property underlying the success of the operations is the ability of furfural to selectively dissolve aromatic and other unsaturated compounds in the presence of aliphatic and other saturated types.

There are, however, a number of ordinary, or non-selective solvent uses for furfural and its derivatives. For the most part, these involve furfural, furfuryl alcohol or tetrahydrofurfuryl alcohol as solvents in the preparation of industrial coatings, dye solutions for textile printing, automotive sludge removers, and paint and varnish removers. Also important are the growing markets for the first two compounds as reactive solvents for urea and phenolic resins.

Furfural dissolves a wide variety of chemical compounds (Chapter 8), including many natural and synthetic polymeric materials. Its low vapor pressure at ordinary temperatures and low toxicity insure safe and easy handling in industrial operations. Where light color is important, however, solvent uses are limited to a certain extent by the amber color of furfural, and are generally confined to applications where lighter colored solvents fail to meet requirements at comparable cost. For example, in coating copper wire with compositions which contain furfural as a component of the solvent mixture, the final baked film is usually darker than the film laid down from certain other solvent systems. On the other hand, it has been noted frequently that furfural imparts improved properties to the film, particularly with respect to adhesion and water-resistance. Where the

odor of furfural is objectionable, it is of interest to point out that, on occasion, this has been successfully masked by the use of additives, such as turpentine, pine oil and alkylated phenols.

To a certain extent, these remarks also apply to furfuryl alcohol, although in this instance there is less odor problem. Tetrahydrofurfuryl alcohol presents no problem with regard to either odor or color, and is likewise a good solvent.

Furfural as a Selective Solvent

In this section, various selective solvent applications are discussed in some detail and the reader will recognize quickly that the basic technique of this type of operation is repeated with appropriate variations for each industry. It must be recognized, however, that industries employing these processes have accumulated a large amount of "know-how" and in many cases, special techniques or refinements of operation are used which are considered secret. No attempt is made in these pages to describe the former, and an effort has been made to exclude anything approaching the latter.

Wood Rosin Purification

The first tank car shipment of furfural was made in 1928 to the Hercules Powder Company for use in its naval stores plant in Brunswick, Georgia. This shipment was an event of major importance for the infant furfural industry. It was no less important for the age-old naval stores industry, for it meant a solution of the problem of recovering high-grade rosin from stumps of cut-over pine lands in the South.

For many years, these stumps had yielded an F grade rosin, dark amber in color, clean and of reasonably uniform consistency. The dark color prohibited its use in soaps, varnishes, and sizing of any but the darkest grades of paper. Much effort was spent in attempts to remove this color and eventually one process produced a light-colored rosin, but even this particular product contained compounds which reacted with alkalies to form color bodies highly objectionable in soaps. In this instance, therefore, solution of the problem of visible color only uncovered the presence of latent color bodies which still limited markets for this improved rosin.

Attempts were then made to precipitate color bodies from solutions of rosin in gasoline without much success. Finally it was found that furfural selectively extracted the color bodies from the gasoline solution and, no less important, the rosin recovered from the gasoline was observed to be substantially free of latent color bodies.

In the language of patents,[1] the process is the refining of wood rosin

[1] Kaiser and Hancock (to Hercules Powder Co.), U. S. Pat. 1,715,088 (1929); *C. A.*, **23**, 1001, 3589 (1929).

"by treatment of the rosin with two liquids which are substantially immiscible at some definite temperature and one of which will be a solvent of the rosin (abietic acid), but not of the color bodies and more especially of the latent color bodies." Specifically, F grade rosin is dissolved in gasoline; furfural is added and the mixture is heated until the two liquids become miscible. The solution is then cooled to 60°F. and the lower, furfural, layer is withdrawn. The furfural is removed by distillation, leaving very dark rosin. The gasoline layer, containing some furfural, is distilled leaving a residue of pale rosin, which can be subjected to another furfural extraction to obtain a "purified" rosin.[2]

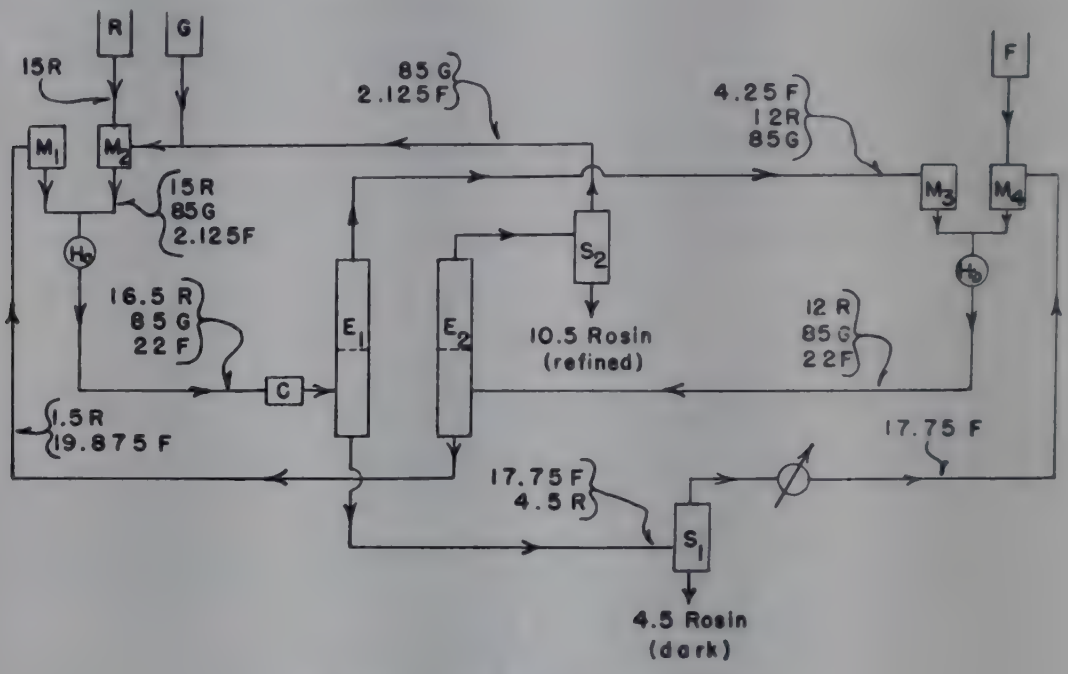


Figure 1. Refining Wood Rosin[3]

F—Furfural
R—Rosin
G—Gasoline
M_1—Furfural surge tank
M_2—Rosin solution tank
M_3—Raffinate surge tank
M_4—Fresh solvent surge tank
H_a and H_b—Homogenizing mixers
C—Cooler
E_1 and E_2—Extraction towers
S_1 and S_2—Evaporators

A simplified flow diagram is given in Figure 1, illustrating a two-stage extraction. While the data are more illustrative than accurate, and are based on certain assumptions which are not borne out in practice, they serve to give a better understanding of the process. Molten rosin is dis-

[2] Kaiser and Hancock (to Hercules Powder Co.), U. S. Pat. 1,715,085 (1929); *C. A.*, **23**, 3588 (1929).

solved in gasoline in M_2 and this solution is mixed with furfural from M_1 in homogenizer H_1. A practically homogeneous mixture (115–120°F.) is discharged from H_1 into extractor E_1 which already contains furfural. The gasoline, now fully cooled, separates from the furfural and rises, carrying with it abietic acid which is insoluble in furfural. This gasoline-rosin solution, partly freed of visible and latent color bodies, eventually passes into M_3, carrying with it a small amount of furfural. The bottoms from E_1, consisting of a furfural solution of color bodies and such other solubles as phenolic compounds, is withdrawn to evaporator S_1 where furfural is recovered and sent to M_4. The dark rosin from S_1 is further treated and marketed under the trade name "Vinsol."

The rosin-gasoline solution in M_3 is homogenized with furfural from M_4 and the extractive purification step is repeated in E_2. In this unit, substantially all of the remaining color bodies are removed. The resulting pale rosin-gasoline solution is discharged from the top of E_2 and the gasoline is evaporated in S_2, from which pale rosin is continuously removed as bottoms.

Many factors affect the efficiency of the process, including the ratio of furfural to rosin, the degree of cooling, the temperature in towers E_1 and E_2, the rate of circulation, and finally, the number of extractions. The rosin extract contains phenolic compounds which can react with furfural. To minimize this potential loss of furfural, it is now plant practice to subject the rosin to one or more preliminary furfural washes before the products are heated to the point of complete miscibility.[4]

In commercial practice, a petroleum naphtha solution of rosin is extracted countercurrently in a Lister refining tower, which is about 40 feet high, 3 feet in diameter, and is divided by fine mesh screening into chambers about 8 inches high. A good description of the solvent refining of wood rosin together with the data in Table 1 is given by Humphrey.[5]

Other furans have been suggested for rosin refining, for example, methyl furfuryl ether, benzyl furfuryl ether,[6] furfuryl acetate, *n*-propyl furoate, and ethyl furoate dissolved in furfural.[7] Humphrey[5] has stated that a good selective solvent should be:

(1) A good solvent for the color bodies.

(2) Quickly and easily separable from the refined rosin phase.

[3] Hancock and Langmeier (to Hercules Powder Co.), U. S. Pat. 2,070,125 (1937); *C. A.*, **31**, 2458 (1937).

[4] Sheffield (to Hercules Powder Co.), U. S. Pat. 2,094,503 (1937); *C. A.*, **31**, 8966 (1937).

[5] Humphrey, *Ind. Eng. Chem.*, **35**, 1062 (1943).

[6] Humphrey (to Hercules Powder Co.), U. S. Pat. 1,905,173 (1933); *C. A.*, **27**, 3628 (1933).

[7] Humphrey (to Hercules Powder Co.), U. S. Pat. 1,890,086 (1932); *C. A.*, **27**, 1774 (1933).

TABLE 1. CHARACTERISTICS OF COMMERCIAL WOOD ROSINS AND EXTRACTED RESINS[5]

Grade	Approx. Lovibond Color*	Acid No.	Saponification No.	Unsaponifiable (%)	Methoxyl (%)	Gasoline Insoluble (%)	Softening Point (°C.)		Refractive Index (20°C.)	Density (20°C.)
							Hercules Drop	Ring and Ball		
Wood rosins										
Crude	80A + 190R	150	170	8.5	1.7	25	86	74	1.56	1.10
Refined										
H	40A + 8R	162	169	7.5	—	0.05	81	72–5	1.5470	1.069
I	40A + 4.5R	163	171	7.5	0.50	trace	82	72–5	—	1.069
K	40A + 2.5R	164	171	7.0	0.45	trace	82	72–5	1.5453	1.069
M	40A + 0.75R	165	171	7.0	0.35	trace	82	72–5	—	1.067
N	39A	165	172	6.0	0.30	trace	83	73–8	—	1.067
WG	27A	166	172	6.0	0.20	trace	83	73–8	1.5453	1.067
X†	12A	171	174	7.0	—	nil	82	73–8	1.5450	1.065
Extracted resins										
Primary	too dark	90	160	8.0	5.5	95	114	102	1.58	1.21
Secondary	too dark	119	150	12.0	3.5	64	83	73	1.58	1.15

* A = amber, R = red (⅓-inch standard cube).

† By reduced pressure distillation of I grade.

(3) Readily separable from the extract.
(4) Non-reactive with rosin or rosin extract.
(5) Non-corrosive, non-toxic, and readily available at low cost.

Furfural meets these requirements in all respects. With reference to the extracting of latent color bodies in crude rosin, Humphrey[6] calls attention to the superiority of furan compounds as compared to aliphatic and aromatic types.

Naval stores production, one of the oldest chemurgic industries, has now been linked to furfural, one of the youngest. A special advantage of this linkage accrues to agriculture. Since the advent of furfural-refining boosted wood rosin sales, the demand for pine stumps has grown to the point where about 200,000 acres of stump land are cleared each year.[8] This waste land is being profitably reclaimed for useful purposes.

Refining Petroleum Oils

Lubricating Oils. Crude petroleum is a complex mixture of cyclic and open-chain, saturated and unsaturated hydrocarbons, together with smaller amounts of nitrogen, oxygen and sulfur compounds. These components are grouped broadly under four classifications, (1) asphalts, (2) naphthenes, and aromatics, (3) paraffins, and (4) waxes which, of course, are not equally suitable for the production of lubricating oils. The asphaltic constituents are solids or very viscous liquids at ordinary temperatures, which property alone makes them unsuitable. In general, the aromatics exhibit low degree of "oiliness", poor resistance to oxidation, and sharp change in viscosity with temperature. Excluding the waxes, which can be precipitated by chilling and removed by filtration, the paraffinic fractions represent the desirable components of lubricants; the viscosity of these fractions is much less affected by change in temperature than that of the aromatics.

The determination of the viscosity-temperature characteristics of an oil is a means of measuring its relative "paraffinicity." Two scales for this purpose are in common use, the Viscosity-Gravity Constant (V.G.C.),[9] and the Viscosity Index (V.I.).[10] The two scales read in opposite directions; a high V.I., and low V.G.C., indicates an oil of relatively high "paraffinicity." It is the objective of the manufacturer to produce lubricating oils of as high a V.I. as possible, due regard being given to end-use and economic factors. One of the best means for improving the V.I. of oils involves treatment with selective solvents, which simultaneously reduce the sulfur content, lower the carbon residue, and increase the response of the oil to additives.

[8] Schantz and Marvin, *Ind. Eng. Chem.*, **31**, 585 (1939).
[9] Hill and Coats, *Ind. Eng. Chem.*, **20**, 641 (1928).
[10] Dean, Bauer and Berglund, *Ind. Eng. Chem.*, **32**, 102 (1940).

As early as 1923, Gohre[11] (see also [12]) suggested the use of furfural for the removal of sulfur compounds from mineral oils. The effect of extracting various oils with an equal volume of furfural at $-10°$ is shown in Table 2.

The first United States patent on the use of furfural as a selective solvent was issued in 1925[13] (see also [14]), and in the specification is to be found the following sentence. "The term 'furfurol derivatives' means those derivatives of furfurol which are present as admixtures in furfurol obtained from cellulose, and which perhaps in the future may be obtained in still greater quantities than they are today." When this was written, the only existing plant for producing furfural had a capacity of about 500 lbs./day. A modern unit for refining lubricating oils may circulate 7,000,000 lbs. of furfural daily. Yet a further illustration of changed conditions is furnished by the salesman who, in 1930, suggested the use of furfural as a selective solvent to one of the larger petroleum companies. The answer to the suggestion

Table 2. Effect of Treating Sulfur-Containing Oils with Furfural[11]

	Brown coal tar oil (% S)	Crude paraffin oil (% S)	Petroleum paraffin oil (% S)
Original oil	1.327	0.987	1.152
Raffinate (insol. in furfural)	0.889	0.558	0.723
Extract (sol. in furfural)	1.598	1.199	1.376

was, "We don't need any selective solvents for our oils. We never expect to need any, and if we did, furfural would not be suitable."

Others believed differently and, in 1933, a subsidiary of The Texas Company, The Indian Refining Company, started the first plant unit using furfural for refining lubricating oils. The process rapidly became widespread and licensees of Texaco Development Corporation all over the world are now using furfural. A list of these plants is given in Table 3. In addition, a number of other plants are in the planning stage.

Although furfural is the only furan compound used commercially in solvent refining, a number of its derivatives have been suggested for this purpose, including the homologous 5-methylfurfural,[15] furyl alkyl ketones,[16]

[11] Gohre, *Petroleum Z.*, **23**, 73 (1923).
[12] Steinbrecher, *Braunkohlenarch.*, No. **31**, 1 (1930); *C. A.*, **26**, 2848 (1932).
[13] Eichwald, U. S. Pat. 1,550,523 (1926); *C. A.*, **20**, 108 (1926).
[14] Oelwerke Stern-Sonneborn A.-G. and Eichwald, German Pat. 399,628 (1925).
[14a] Smoley, *Petroleum Processing*, **3**, No. 8, 735 (1948).
[15] Govers (to Indian Refining Co.), U. S. Pat. 2,137,206 (1939); *C. A.*, **33**, 1485 (1939).
[16] Clark (to Texas Co.), U. S. Pat. 2,020,290 (1936); *C. A.*, **30**, 604 (1936).

TABLE 3. SOLVENT EXTRACTION PLANTS USING FURFURAL*

Refinery	Location	Estimated Charge Capacity (barrels/day)
1. Gulf Oil Corporation	Port Arthur, Texas	6,000
2. The Texas Company	Lawrenceville, Illinois	2,400
3. The Texas Company (4 units)	Port Arthur, Texas	16,000
4. Magnolia Petroleum Company (2 units)	Beaumont, Texas	7,200
5. Shell Oil Company	Martinez, California	3,250
6. Quaker State Refining Company	Farmer's Valley, Pennsylvania	1,700
7. Quaker State Refining Company	St. Mary's, West Virginia	600
8. Quaker State Refining Company	Emlenton, Pennsylvania	1,700
9. Continental Oil Company	Ponca City, Oklahoma	1,500
10. Golden Bear Oil Company	Bakersfield, California	500
11. Cooperative Refinery Association	Coffeyville, Kansas	2,000
12. Socony-Vacuum Oil Company, Inc.	Paulsboro, New Jersey	4,950
13. Tide Water Associated Oil Company	Bayonne, New Jersey	5,000
14. Sun Oil Company	Marcus Hook, Pennsylvania	2,000
15. Cit-Con Oil Corporation	Lake Charles, Louisiana	8,000
16. Standard Oil Company of Ohio	Lima, Ohio	5,000
17. British American Oil Company, Ltd.	Clarkson, Ontario, Canada	2,000
18. Shell Refineries, Ltd.	Shell Haven, England	1,650
19. Anglo-Iranian Oil Company†	Llandarcy, England	1,400
20. Anglo-Iranian Oil Company†	Kent, England	4,500
21. Vacuum Oil Company†	Coryton, England	2,000
22. Gewerkshaft "Nerag"	Hanover, Germany	3,000
23. Anglo-Iranian Oil Company	Abadan, Iran	1,500
24. Companie Espanola de Petroleo S.A.	Tenerife, Canary Islands	900
25. Societe General Huiles de Petrole	Dunkirk, France	2,000
26. Compagnie Francaise Raffinage	Gonfreville, France	5,000
27. Vacuum Oil Company	Gravenchon, France	2,000
28. Shell Oil Company	Cardon, Venezuela	6,000
29. Shell Oil Company	Curacao, British West Indies	5,000
30. Raffineri de Napoli	Naples, Italy	1,000
31. Raffineri Olii Lubrificanti†	Milan, Italy	300
32. "Aquila" S.A.	Trieste, Italy	1,100
33. Nippon Oil Company (2 units)†	Kudamatsu, Japan	700
34. Mitsubishi Oil Company†	Kawasaki, Japan	1,000
	Total	108,850

* The majority of this material is taken from Smoley,[14a] and brought up-to-date from information in the files of The Quaker Oats Company.

† Under construction.

butyl furoate,[17] furonitrile,[18, 19] tetrahydrofuran,[20] tetrahydrofurfural,[21] furfuryl and tetrahydrofurfuryl alcohols,[22, 23, 24] and such derivatives as furfurylamine[25] and tetrahydrofurfuryl acetate.[26] Most of these compounds are unavailable in the quantities required. All are, in general, too expensive for use in this particular field.

The patent literature also contains many suggestions for using adjuvants with furfural, for example, propane, benzene or xylene, naphthalene, chlorophenols, amylamine, acetonitrile, trichloroethane and octyl aldehyde. However, the use of furfural alone is the most economical practice.

Characteristics Which Make Furfural a Good Refining Agent. Furfural is a good refining agent for petroleum oils because it is:

(1) Highly selective. It has the ability to dissolve the undesirable components, but very limited solubility for the paraffinic fractions.

(2) Effective at reasonable operating temperatures.

(3) Liquid at ordinary winter temperatures, thus avoiding operating complications in cold weather.

(4) Readily separable from both raffinate and extract.

(5) Non-toxic under normal operating conditions.

(6) Stable under the conditions of use.

(7) Non-corrosive.

(8) Adaptable to a wide range of crude stocks.

(9) Available at low cost, and in large quantities from annually replenished raw materials.

Those readers who are particularly interested in the question of selectiv-

[17] Henderson (to Atlantic Refining Co.), U. S. Pat. 2,030,870 (1936); *C. A.*, **30**, 2362 (1936).

[18] Dietrich (tg E. I. du Pont de Nemours & Co.), U. S. Pat. 2,188,531 (1940); *C. A.*, **34**, 4561 (1940).

[19] Hixson and Miller (to Chemical Foundation Inc.), U. S. Pat. 2,204,758 (1940); *C. A.*, **34**, 7596 (1940).

[20] Pevere (to Texas Co.), U. S. Pat. 1,998,399 (1935); *C. A.*, **29**, 3820 (1935).

[21] Inoue and Nisimoto (to Settu Seiyu K. K.), Japanese Pat. 131,260 (1939); *C. A.*, **35**, 2314 (1941).

[22] Hill (to Atlantic Refining Co.), U. S. Pat. 1,883,374 (1933); *C. A.*, **27**, 836 (1933).

[23] Texaco Development Corp., French Pat. 761,270 (1934); *C. A.*, **28**, 4218 (1934).

[24] Detwiler (to Texaco Development Corp.), Canadian Pat. 347,767 (1935); *C. A.*, **29**, 3148 (1935).

[25] Salzberg (to E. I. du Pont de Nemours & Co.), U. S. Pat. 2,088,411 (1937); *C. A.*, **31**, 6863 (1937).

[26] Hendrey and Cook (to Texas Co.), U. S. Pat. 2,141,605 (1939); *C. A.*, **33**, 2697 (1939).

TABLE 4. FURFURAL REFINING OF LUBRICATING OIL STOCKS FROM VARIOUS CRUDE SOURCES[28]

Crude source	East Texas	East Texas	Illinois	Oklahoma City	Oklahoma City	Gulf Coast	California	Pennsylvania	Arabia	Arabia	Venezuela
Grade	Light neutral distillate	Deasphalted bright stock residuum	Medium viscosity distillate	Light neutral distillate	Intermediate viscosity distillate	Medium viscosity distillate (nonwaxy)	Light neutral distillate (nonwaxy)	Cylinder stock	Light neutral distillate	Deasphalted residuum	Deasphalted bright stock residuum
Physical characteristics											
Charge oil											
gravity, ° A.P.I.	28.3	23.1	24.7	27.6	25.4	20.8	20.1	25.4	25.0	20.1	23.3
viscosity at 210°F. S.S.U.	41.0	132.6	53.3	45.7	69.3	53.3	40.7	165.6	42.4	128.9	175.0
viscosity index	—	—	—	—	—	26.5	−25	—	—	—	—
carbon residue, %	0.07	1.40	0.14	0.04	0.52	0.17	0.05	1.98	0.09	2.27	1.02
pour point, °F.	—	—	—	—	—	−25	−25	—	—	—	—
Raffinate											
gravity, ° A.P.I.	32.5	29.6	32.5	33.3	30.9	24.7	27.5	27.6	30.6	26.6	26.7
viscosity at 210°F. S.S.U.	40.4	102.3	47.9	43.5	58.4	53.0	40.9	149.5	41.4	109.2	147.4
viscosity index	—	—	—	—	—	61.0	49.0	—	—	—	—
carbon residue, %	0.01	0.20	0.01	0.01	0.03	0.07	0.01	0.97	0.02	0.74	0.26
pour point, °F.	—	—	—	—	—	−25	−25	—	—	—	—
Dewaxed raffinate											
gravity, ° A.P.I.	29.8	27.2	31.2	31.5	29.7	—	—	27.1	28.4	25.5	25.9
viscosity at 210°F. S.S.U.	43.0	140.6	49.9	45.4	63.2	—	—	161.0	43.4	122.4	174.7
viscosity index	96.0	94.1	102.0	96.5	96.0	—	—	103.5	96.5	98.8	95.8
pour point, °F.	20	0	0	0	0	—	—	10	−5	10	10
Extract gravity, ° A.P.I.	8.0	13.9	13.2	8.8	9.5	6.8	9.5	7.9	5.6	9.5	9.6
Refining conditions											
Amount furfural applied, % by vol.	124	507	349	263	264	174	223	247	101	445	360
Temp., °F.											
raffinate outlet zone	200	290	264	224	265	165	159	271	183	250	260
extract outlet zone	140	233	190	149	190	101	101	191	119	175	195
Raffinate yield, % by vol.	85.0	60.9	64.2	82.4	76.9	80.2	61.6	90.1	80.4	65.7	81.6

ity may wish to refer to a published investigation[27] in which a total of 110 different solvents were studied, and data on the viscosity-gravity constants of the extracts and raffinates were reported. Furfural ranked among the best of the solvents tested.

It is beyond the scope of this book to give detailed consideration to the results obtained by refining oils with furfural. Involved in such a discussion would be changes effected in such characteristics as viscosity index, color, carbon residue, oxidation, stability, etc. Each refinery has its own special problems and particular objectives, and numerous tables of performance data from various plants have appeared in the literature. Some idea of the flexibility of the furfural process can be gained, however, from the figures listed in Table 4.

Furfural Solvent Refining Unit. The basic elements in a furfural refining unit for extraction of oils are four, (1) the extraction tower, (2) the raffinate mix tower in which the oil is freed from furfural, (3) the extract mix towers in which furfural is freed from the extract, and (4) the solvent recovery section. Descriptions and flow charts of such plants have appeared in the literature on a number of occasions.[29, 30, 31, 32, 33, 28] The flow diagram of Figure 2 is from Kemp *et al.*,[28] who also give tabulated data showing the effects, on raffinate and extract, of changes in such factors as solvent-charge ratio, temperature, and reflux ratio, among others.

In the following description of operations, only the main flow of raffinate, extract, wet and dry solvent will be traced, omitting mention of the numerous heat exchangers and coolers. While the proper operation of these units is vital to both efficiency and economy of operation, it is not within the scope of this book to consider the engineering aspects of a plant such as that outlined in Figure 2.

Hot charge oil is introduced through a distributor to packed sections of the extraction tower where it becomes mixed with the down stream of furfural. The oil phase containing about 10 per cent solvent and called

[27] Ferris, Birkhimer and Henderson, *Ind. Eng. Chem.*, **23,** 753 (1931).
[28] Kemp, Hamilton and Gross, *Ind. Eng. Chem.*, **40,** 220 (1948).
[29] Manley, McCarty and Gross, *Oil Gas J.*, **32,** No. 23, 78, 79, 81, 82 (1933).
[30] *Chem. Met. Eng.*, **47,** 859 (1940).
[31] Mertens, *Oil Gas J.*, **39,** No. 26, 47 (1940).
[32] A Staff Report (British American Oil Co., Ltd.), *Can. Chem. Process Inds.*, **27,** No. 12, 669 (1943).
[33] Smoley and Fulton, *Petroleum Processing*, **2,** 594, 597, 602, 605, 608 (1947).

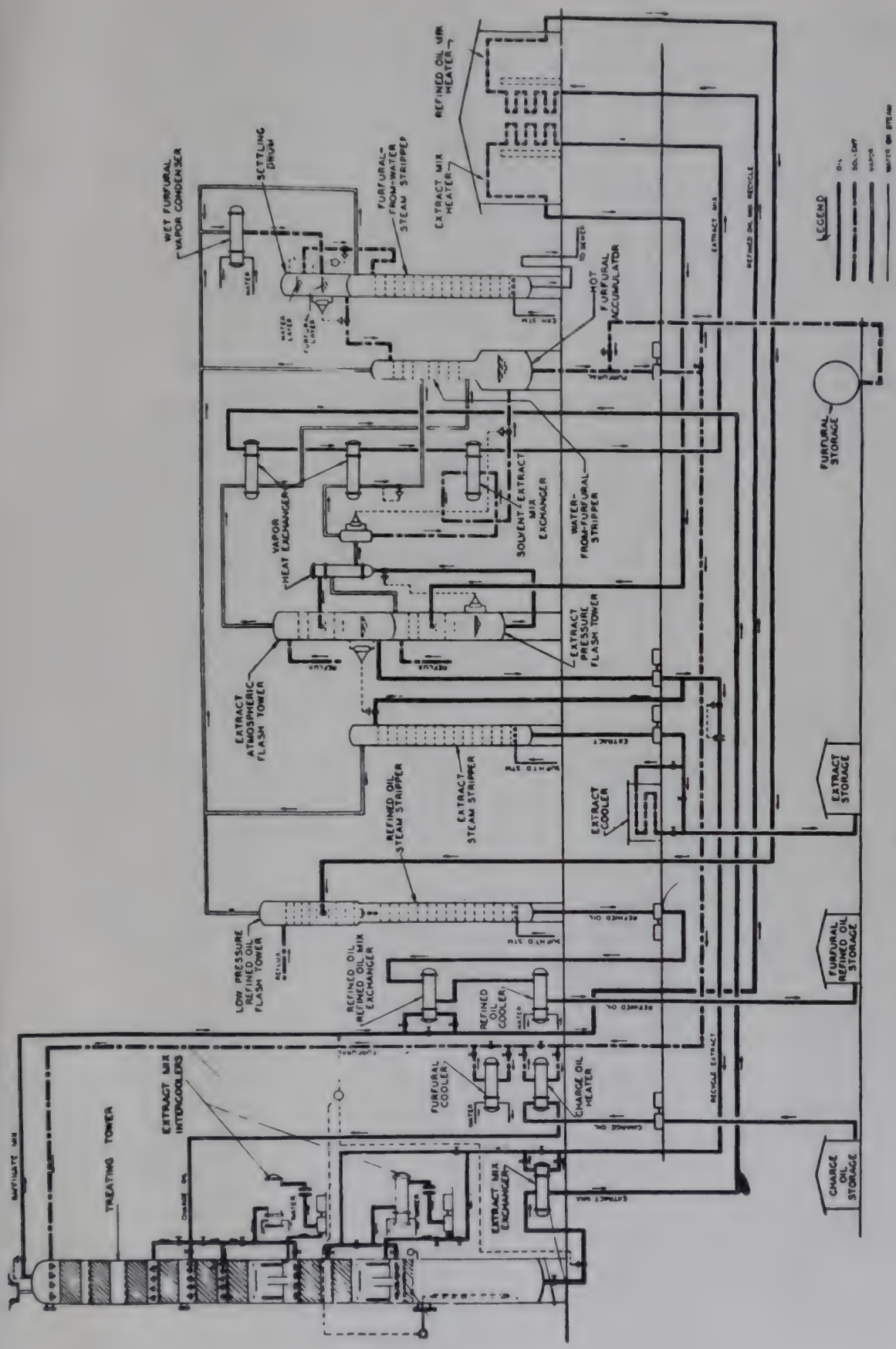


Figure 2. Furfural Refining Unit[28]

"raffinate mix" is removed overhead, passed through a heater and flashed into the low-pressure refined oil flash tower. The oil, stripped of most of its solvent, drops to a lower section where the final traces of furfural are removed by means of superheated steam. The bottoms, which is refined oil, is cooled and sent to storage. The solvent vapor with the steam used for stripping is taken to the wet furfural condenser.

The extract mix leaving the bottom of the extractor consists of about 90 per cent furfural and 10 per cent of "undesirable" components of the original stock. The solvent is recovered from this mix by flashing, at about 450°F. and 25–30 p.s.i., into the extract-pressure flash tower. The furfural vapor from this tower generally contains a little moisture picked up from the oil in the extraction tower. It could be sent to the wet-furfural condenser, but in the process outlined in Figure 2 it is, instead, partially condensed. The condensate, which is anhydrous furfural, goes directly to the furfural accumulator. The uncondensed, wet-furfural vapor passes to the water-from-furfural stripper.

The extract from the pressure tower, now considerably leaner in furfural, is sent to another flash tower, this one operating at atmospheric pressure. The furfural vapor from here is essentially dry and is sent to the bottom of the water-from-furfural stripper.

The extract is now almost free from solvent. A portion of it (recycle extract) is used as reflux to "salt out" oil in the lower section of the extraction tower. The last traces of furfural are removed from the final outgoing extract in the extract-steam stripper.

It remains to describe the separation and recovery of furfural from the water introduced, largely, in the steaming operations in the refined oil and extract steam-strippers. The wet vapors are condensed and led to a settling drum wherein the condensate separates into two layers. The upper, aqueous phase which is saturated with furfural is fed into the upper section of the furfural-from-water steam stripper from which a minimum boiling furfural-water azeotrope (p. 319) is taken overhead to the wet-furfural condenser. The bottoms from this column, entirely freed from solvent, goes to waste.

The lower, furfural layer in the settling drum contains 92–95 per cent furfural and 8–5 per cent water. This is the feed for the water-from-furfural stripper. As it passes down the column its water content is stripped overhead as the furfural-water azeotrope. Anhydrous furfural is taken from the bottom into the accumulator for reuse or storage.

Solvent Losses. Furfural is a thermally-stable aldehyde.[34] In storage, or in distillation operations even at high temperature, its rate of decomposition

[34] Dunlop and Peters, *Ind. Eng. Chem* , **32**, 1639 (1940).

in an inert atmosphere is extremely small. In a well-designed unit for refining lubricating oils, physical losses (liquid and vapor leaks) of furfural can be kept in the range of 0.005–0.01 per cent of the total quantity in circulation. On the other hand, some oil stocks subjected to refining operations contain acidic substances, phenolic bodies, and reactive sulfur and nitrogen compounds which can react with furfural, particularly at the elevated temperatures generally employed. Losses of solvent due to such reaction may, in some instances, be greater than the physical losses.

The over-all solvent loss in one large refinery is 0.015 per cent of the solvent circulated, but this is probably better than the industry average. In extractive distillation plants, solvent loss is between 0.01 and 0.02 per cent of the total circulated, and in rosin refining, the loss is about one per cent based on the weight of purified rosin. When laymen hear of these low furfural losses, they generally feel that the over-all consumption of furfural by petroleum refiners is negligible. However, it was mentioned earlier that a single refinery may circulate as much as 7,000,000 lbs. of furfural per day. At 0.02 per cent loss, this represents a furfural make-up of 1400 lbs./day. Therefore, in spite of the low solvent losses, the petroleum industry is the second largest consumer of furfural.

Gas Oils—Diesel Fuels. Gas oils are used for making Diesel fuels, domestic heating oils and as catalytic cracking charge stocks. Due to the widespread use of cracking processes, however, the supply of straight run fuels is inadequate to meet the ever-growing demand, and the blending of cracked fuels to augment the supply introduces complications. That is, many cracked gas oils contain considerable amounts of sulfur and, in general, all require up-grading to improve burning quality. The problem is quite similar to that involved in improving the quality of lubricating oils (p. 737) and has found a similar solution, namely, solvent refining[35, 28] (see also [36]).

The first commercial plant for treating catalytic cycle gas oils with furfural for the production of Diesel and furnace oils was that of The Texas Company at Eagle Point, New Jersey. Like the lubricating oil refining unit discussed previously, this installation has a countercurrent extraction tower, raffinate and extract strippers and solvent recovery systems, but in other respects the two plants differ widely. The ratio of solvent to charge stock is much lower for refining Diesel fuels than for lubricating oils, and the furfural recovery system differs from that in the lubricating oil refinery since the boiling ranges of Diesel fuels are much lower than are encountered with lube oils.

[35] Dryer, Chenicek, Egloff and Morrell, *Ind. Eng. Chem.*, **30**, 813 (1938).

[36] Feigin, Obleukhova and Prorokov, *Neftyganoe Khoz.*, **1936**, No. 3, 57; *C. A.*, **31**, 4093 (1937).

Gas oils of similar quality, whether virgin stocks or cracked cycle gas oils derived therefrom, are equally amenable to refining with furfural. This is indicated by the data in Table 5 which illustrate the degree of cetane-number improvement obtained when the furfural process was applied to virgin and cracked stocks from several sources.[37]

Gross *et al.*[37] also present data showing the extent of sulfur removal (Table 6), and the improvement in burning-oil characteristics (Table 7) as a result of furfural refining of virgin gas oils and catalytically cracked cycle stocks.

Extractive Distillation

Separation and Purification of C_4 Hydrocarbons. During World War II the manufacture of GR-S synthetic rubber required production of enormous quantities of relatively pure 1,3-butadiene. This diolefin was available at low cost, as a minor component of cracked refinery gases, but a major problem was its concentration to a purity of 98.5 to 99.5 per cent. One solution was the use of extractive distillation with furfural. Three such units were built during the war: one by Phillips Petroleum Company near Borger, Texas, with a yearly butadiene capacity of 56,200 tons; one by Sinclair Rubber, Inc., at Houston, Texas, with a capacity of 62,500 tons, and the third (capacity 125,000 tons), by Neches Butane Products Company at Port Neches, Texas. This latter company is a non-profit organization owned by five oil companies: The Texas Company, Gulf Oil Corporation, Socony-Vacuum Oil Company, Inc., Atlantic Refining Company, and The Pure Oil Company.

These three plants using furfural have an annual capacity of 243,500 tons, about 54 per cent of the total butadiene capacity in this country in 1949. Bohmfalk[37a] estimates the cost of butadiene to be about 12.5 cents per pound, allowing 25 per cent return (before taxes) on the capital invested and operation at 80 per cent of capacity.

The basic principles governing the operation of all three plants were similar but somewhat different feed stocks were used. The first step in the Phillips plant was the dehydrogenation of *n*-butane to form *n*-butylenes, whereas the Neches unit started with a mixture of refinery butene gases containing isobutane, *n*-butane, 1-butene and isobutene.[38] This mixture or the product from the *n*-butane dehydrogenator was separated into streams rich in *n*-butenes which were dehydrogenated, and butadiene was recovered from the resulting product. Among the products which had to be handled

[37] Gross, Skelton and Best, *Oil Gas J.*, **48**, No. 46, 211 (1950).

[37a] Bohmfalk, *Chem. Eng. News*, **28**, No. 30, 2504 (1950).

[38] Neches Technical Committee (Eastman *et al.*), *World Petroleum*, **64**, No. 4, 54 (1945).

TABLE 5. FURFURAL REFINING GAS OILS—CETANE NUMBER IMPROVEMENT[37]

Crude source	Virgin stocks						Cracked stocks					
	Venezuela		California		East Texas		Arabian		Venezula		California	
	charge	raffinate	charge	raffinate	charge	raffinate	charge	raffinate	charge	raffinate	charge	raffinate
Yield, volume %.....	100	66.6	100	95.0	100	82.0	100	60.0	100	60.5	100	65.5
Cetane number.....	34.4	49.6	46.2	50.6	53.2	62.9	19.0	61.0	33.6	53.0	37.7	55.1
Gravity, ° A.P.I.....	24.2	30.8	28.9	30.6	33.9	37.8	20.2	40.4	24.5	33.6	29.7	38.8
Color, N.P.A.....	7	3+	—	—	—	—	2.5−	1.5−	7	1−	—	—
Sulfur, weight %.....	0.80	0.37	0.98	0.72	1.12	0.49	1.705	0.451	0.58	0.09	0.50	0.06

at these plants were all of those listed in Table 8 and, in addition, hydrogen, methane, ethane, propane, propene, and many more. From the table it can

TABLE 6. FURFURAL REFINING GAS OILS—SULFUR REMOVAL[37]

Crude source	Virgin stocks				Cracked stocks				
	West Texas		Poza Rica		Arabian		paraffinic and mixed naphthenic		
	charge	raffinate	charge	raffinate	charge	raffinate	charge	raffinate	raffinate
Yield, volume %	100	69.0	100	92.4	100	78.9	100	70.0	50.0
Sulfur, weight %	1.31	0.68	0.97	0.58	1.39	0.39	0.833	0.51	0.137
Gravity, ° A.P.I.	27.0	33.0	36.4	39.4	32.0	40.5	24.0	29.9	37.0
Cetane number	52.5	69.5	59	66	44.8	62.5	30.7	42.4	57.4

TABLE 7. BURNING-OIL CHARACTERISTICS[37]

Burning oil	Catalytic cycle gas oil	Furfural refined catalytic cycle gas oil	Virgin reference fuel
Gravity, ° A.P.I.	29.7	39.0	39.3
Burning index (Atlantic method)	53	84	83
B.t.u. per pound	19,400	19,700	19,750
Carbon–hydrogen ratio	7.20	6.26	5.53
Diesel index	38.1	67.0	65.6
Cetane number	39.5	57.7	55.8
Aniline point, °F	128.7	171.9	167.0
Sulfur, %	0.48	0.04	0.05

be seen that there are seven compounds boiling within the comparatively narrow range of 10.9–38.7°F. Some of these can be separated by careful fractionation, but others cannot. *n*-Butane and butadiene form a minimum boiling azeotrope, hence are not separable by conventional fractionation. The problem was solved, however, by a combination of fractional and extractive distillation steps, which permitted the isolation of butadiene of 99.5 per cent purity.

Extractive distillation is defined[39] as "distillation in the presence of a substance which is relatively non-volatile compared to the components to be separated and which, therefore, is charged continuously near the top of the distilling column so that an appreciable concentration is maintained on all plates of the column." Expressed in another way, the presence of the

[39] Benedict and Rubin, *Trans. Am. Inst. Chem. Engrs.*, **41**, 353 (1945).

TABLE 8. SOME C_4 HYDROCARBONS ENCOUNTERED IN THE PRODUCTION OF BUTADIENE[38]

Hydrocarbon	Boiling point (° F.)
Isobutane	10.9
Isobutene	19.6
1-Butene	20.7
1,3-Butadiene	24.0
n-Butane	31.1
trans-2-Butene	33.6
cis-2-Butene	38.7
Vinylacetylene	41.2
Ethylacetylene	47.7

non-volatile solvent distorts the normal volatility ratios existing among the components to be separated. An excellent example of this distortion is indicated by the data (Table 9) of Buell and Boatright.[40] With no solvent,

TABLE 9. RELATIVE VOLATILITIES OF SOME C_4 HYDROCARBONS AND THE EFFECT OF FURFURAL

Hydrocarbon	Relative Volatility*	
	no solvent	furfural + 4% water†
Isobutane	1.209	2.6 (approx.)
Isobutene	1.070	1.666
1-Butene	1.046	1.718
1,3-Butadiene	1.000	1.000
n-Butane	0.871	2.020
trans-2-Butene	0.843	1.190
cis-2-Butene	0.776	1.065

* Volatility is the vapor pressure of the hydrocarbon at 106°F. divided by the vapor pressure of butadiene at 106°F. (65 p.s.i. abs.).

† These ratios were determined at 130°F. (65 p.s.i. abs.).

butadiene is less volatile than the first three hydrocarbons listed, but more volatile than *n*-butane and the isomeric 2-butenes. In the presence of furfural containing 4 per cent water, however, butadiene is the least volatile of all.

American oil and rubber companies did not become particularly interested in extractive distillation until the late 'thirties and the war broke before their work was ready for publication. Because of secrecy restrictions, no patents or publications were issued until 1944. Frey[41] described the separation of ethyl- and vinyl acetylenes from butadiene, and later additional patents were issued specifically directed to the separation of acet-

[40] Buell and Boatright, *Ind. Eng. Chem.*, **39**, 695 (1947).

[41] Frey (to Phillips Petroleum Co.), U. S. Pat. 2,356,986 (1944); *C. A.*, **38**, 312 (1945).

ylenic hydrocarbons.[42, 43] A rather detailed description of the process as actually operated is disclosed in a patent to Hachmuth[44] (see also [45, 46]).

To understand the complex sequence of operations in butadiene purification, it is helpful to consider the first four compounds in Table 8 as group A, and the following five as group B. Members of group A are separated from members of group B by conventional fractional distillation, except *n*-butane and butadiene which, as already noted, form an azeotrope. Separations within a single group are accomplished by extractive distillation. These are:

(1) isobutane from 1-butene (both are in group A).
(2) 1-butene from butadiene (both are in group A).
(3) *n*-butane from 2-butenes (a group B separation).

Figure 3 is a greatly simplified diagram illustrating the separation of isobutane from 1-butene. The mixture is fed at 90 p.s.i.g., and 127°F. to the 41st plate (measured from the top) of a 100-plate column.[47] Solvent (furfural containing 2–4 per cent water) enters at the fifth plate. The top five plates constitute the furfural "knock-back" section; from plate 6 to 41 is the absorbing section in which 1-butene is absorbed from the hydrocarbon mixture; in the lower portion of the column isobutane is stripped from the solvent. The bottoms, rich in 1-butene, passes to a 20-plate column where the hydrocarbon is removed overhead. The solvent, now free of all hydrocarbons, is recycled to the extractive distillation tower.

Instead of the simple mixture of 1-butene and isobutane assumed in

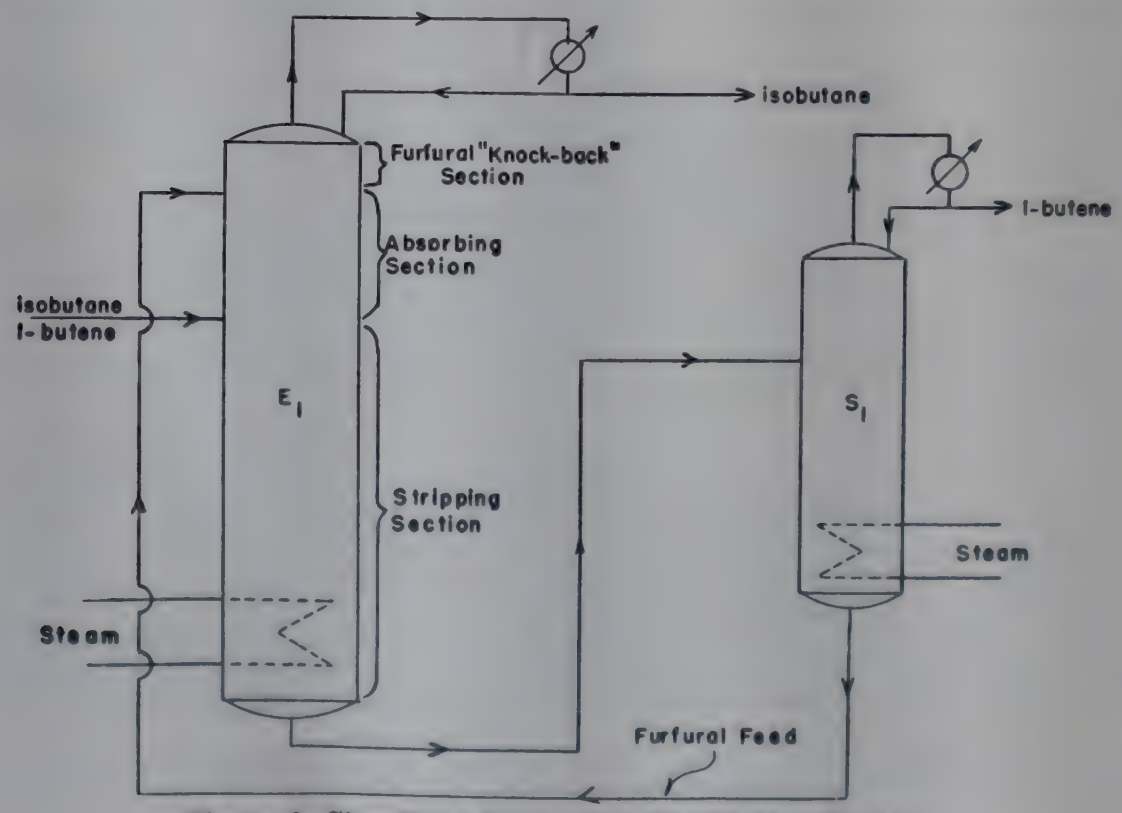


Figure 3. Simplified Extractive Distillation System
E_1—100 plate extraction tower
S_1—20 plate stripping column

this description, actually there are substantial quantities of other hydrocarbons. Table 10 is a condensation of data presented by Happel *et al.*[47] showing the volume and composition of feed, analyses of the condensates from the tops of the extractive distillation tower E_1, and stripping column

TABLE 10. PERFORMANCE DATA ON ISOBUTANE TOWER TEST[47]

Feed Composition (mole %)	Effluents	
	Tower overhead (E_1, Figure 4) (mole %)	Stripper overhead (S_1, Figure 4) (mole %)
Propane-propene (10.4)	17.3	—
Isobutane (33.8)	57.1	0.5
Isobutene (4.7)	0.2	10.2
1-Butene (26.2)	0.7	66.6
1,3-Butadiene (1.1)	0.3	1.4
n-Butane (18.2)	24.0	8.9
trans-2-Butene (4.7)	0.2	10.7
cis-2-Butene (0.9)	0.2	1.7

S_1, respectively (see Figure 4). How well the tower in Figure 3 accomplished its primary purpose of separating isobutane from 1-butene can be seen from these data but possibly even more graphically from Table 11.

TABLE 11. CHANGES IN RELATIVE CONCENTRATIONS[47]

Ratios	Feed	Tower	Stripper
1-Butene/isobutane	0.775	0.012	133.2
Total unsaturates/saturates	0.603	0.016	9.64

Operational Sequences. Figure 4 is a simplified flow diagram of the Neches plant in which E_1 and S_1 represent the same units shown in Figure 3. E_2 and S_2 comprise the extractive distillation unit removing *n*-butane from

[42] Buell (to Phillips Petroleum Co.), U. S. Pat. 2,382,603 (1945); *C. A.*, **39**, 4887 (1945).

[43] Welling (to Phillips Petroleum Co.), U. S. Pat. 2,395,362 (1946); *C. A.*, **40**, 2847 (1946).

[44] Hachmuth (to Phillips Petroleum Co.), U. S. Pat. 2,386,310 (1945); *C. A.*, **40**, 1168 (1946).

[45] Hachmuth (to Phillips Petroleum Co.), U. S. Pat. 2,415,006 (1947); *C. A.*, **41**, 2570 (1947).

[46] Wagner (to Phillips Petroleum Co.), U. S. Pat. 2,415,921 (1947); *C. A.*, **41**, 3287 (1947).

[47] Happel, Cornell, Eastman, Fowle, Porter and Schutte, *Trans. Am. Inst. Chem. Engrs.*, **42**, 189 (1946).

mixtures of the isomeric 2-butenes. The third unit of this kind, represented by E_3 and S_3, separates butadiene from 1-butene. The solvent from all strippers goes to a common surge tank and all solvent feed to the extraction units comes from this tank. About 1–2 per cent of the total circulating solvent is continually withdrawn and distilled to prevent excessive build-up of a high boiling material which is slowly formed in the course of the operation.

The feed to the Phillips plant is *n*-butane[40] which is dehydrogenated primarily to 1-butene and *cis*- and *trans*-2-butenes. Since there is little isobutene and isobutane in the Phillips' streams, one less extractive distillation step is needed. A patent[44] issued in 1945 gives a comprehensive schematic flow diagram of butadiene purification which includes the units shown in Figure 4. This patent as well as articles by Happel *et al.*[47] and Buell and Boatright[40] describe the fate of such minor constituents as propane and acetylenic hydrocarbons, among others. Those interested in the engineering phases of extractive distillation are referred to these papers. Phase data on mixtures of hydrocarbons and furfural are given by Holloway and Thurber.[48]

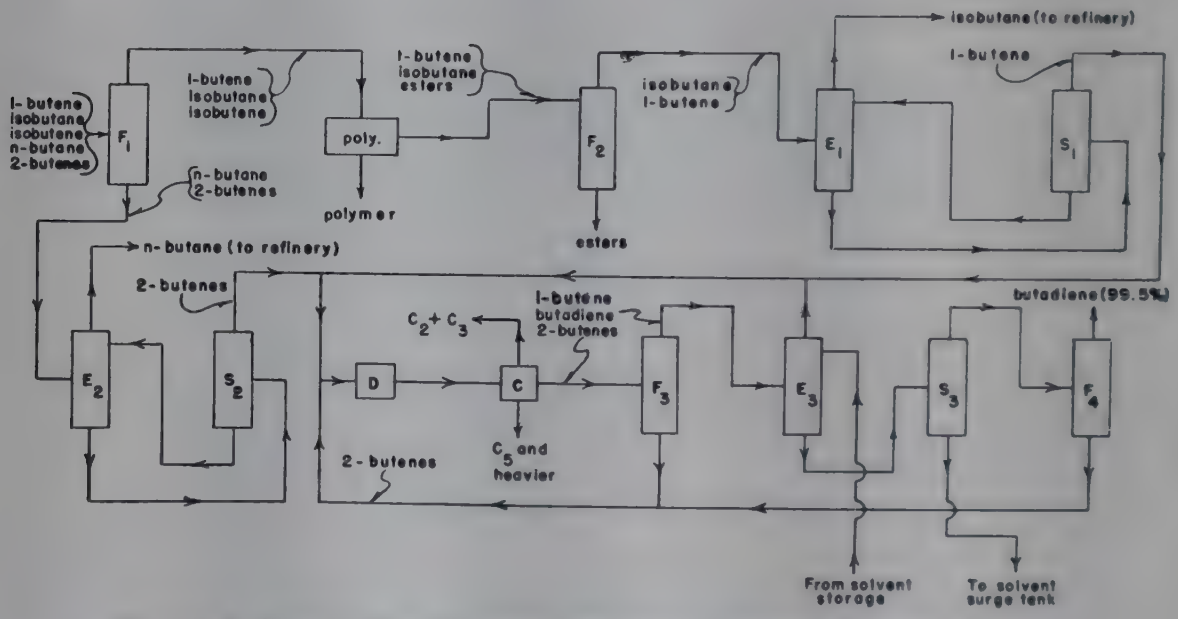


Figure 4. Separation of Butadiene from Refinery Cracked Gases

F—Fractionating columns
E—Extractive distillation columns
S—Solvent strippers
Poly—Polymer unit
D—Dehydrogenator
C—Compressor-depropanizer

In Table 10 test data are given for units E_1 and S_1 (Figure 4). Similar data are given in Tables 12 and 13 for the separation of *n*-butane from the

[48] Holloway and Thurber, *Ind. Eng. Chem.*, **36**, 980 (1944).

2-butenes (units E_2 and S_2), and of butadiene from 1-butene (units E_3 and S_3). All of the data are condensed from the paper by Happel *et al.*[47]

TABLE 12. PERFORMANCE DATA ON *n*-BUTANE TOWER TEST[47]

Feed Composition (mole %)	Effluents	
	Tower overhead (E_2, Figure 4) (mole %)	Stripper overhead (S_2, Figure 4) (mole %)
Isobutane (0.3)	0.5	0.1
Isobutene (0.8)	0.5	1.4
n-Butane (63.8)	98.1	3.5
trans-2-Butene (20.2)	0.7	54.9
cis-2-Butene (14.9)	0.2	40.1

TABLE 13. PERFORMANCE DATA ON BUTADIENE TOWER TEST[47]

Feed Composition (mole %)	Effluents	
	Tower overhead (E_3, Figure 4) (mole %)	Stripper overhead (S_3, Figure 4) (mole %)
Isobutane (0.7)	0.4	0.0
Isobutene (9.9)	14.0	0.0
1-Butene (30.4)	43.5	0.2
1,3-Butadiene (32.3)	6.8	92.9
n-Butane (13.7)	19.2	0.0
trans-2-Butene (11.2)	15.1	3.4
cis-2-Butene (1.8)	1.0	3.5

The butadiene from stripper S_3 is free from other hydrocarbons with the exception of a trace of 1-butene and about 7 mole per cent of the isomeric 2-butenes. The latter are removed by a final fractionation in column F_4.

Choice of Extractive Solvent. Furfural is one of the preferred solvents for the recovery of butadiene by extractive distillation. The factors dictating the particular extractive agent are essentially the same as were mentioned in the section on lubricating oils and rosin. They are (1) selectivity, (2) capacity, (3) volatility, (4) toxicity, (5) cost, (6) availability, (7) stability, and (8) ease of recovery.

Selectivity is measured by the degree by which the relative volatility of one component to another component is changed at a given concentration of the solvent. For example, in comparing the selectivity of furfural against phenol a mixture of 80 mole per cent furfural, 10 mole per cent butadiene, and 10 mole per cent of 1-butene might be made and the relative volatility of 1-butene to butadiene would then be measured. A similar test would be made using 80 mole per cent phenol in place of furfural. Other factors

being equal, the solvent in which the differences in volatilities of 1-butene and butadiene were greatest would be chosen as the most selective. Buell and Boatright[40] state that "of the solvents tested, only furfural, acetone, phenol and water met the requirements of high selectivity for butadiene and commercial availability." Water had the best selectivity but it failed because of (2) above, namely, poor capacity. Because of its negligible solvent power for C_4 hydrocarbons, the volume of water necessary would be quite impractical. Furfural plus water is more selective than furfural alone, hence wet furfural is used instead of anhydrous furfural.[49] Not only is this a more selective solvent but it obviates the necessity of dehydrating furfural after its purification by steam distillation.

The third point to be considered in choosing a solvent, volatility, needs little discussion. The greater the volatility of the solvent compared to the non-solvent, the greater the relative concentration of solvent in the vapor, the poorer the enrichment per tray, and the greater the load placed on the reboiler. The solvent must be separable from the solute by practical means, otherwise both would be unavailable for further use. Furfural-water can be stripped entirely free of C_4 hydrocarbons in comparatively small columns.

Practical operating experience over 20 years is the most cogent evidence regarding the non-toxicity of furfural. No case of disability or physiologic impairment due to handling or exposure to furfural in any solvent plant has come to the authors' attention. This statement should be qualified to except those individuals, of whom there are a few, who are allergic to this aldehyde.

Costs are relative and hence, (5) must be considered in the light of conditions existing where a unit is to be installed. This factor is intimately connected with stability and completeness of recovery. Smith and Braun[50] point out that the small differences between singly unsaturated C_4 olefins and butadiene preclude the possibility of finding the "ideal" solvent, so that the choice rests largely on an economic basis. They describe an apparatus used in investigating solubility and distribution in C_4-solvent systems and present data at 20°F. for the following systems: (1) furfural-isobutene-butadiene; (2) furfural-naphtha-butadiene; (3) furfural-naphtha-isobutene; (4) furfural-butadiene-isobutene-naphtha.

The factors of stability and ease of recovery may be considered together. Published figures indicate total furfural losses in the Phillips plant to be 0.01 to 0.02 per cent of total solvent circulation, and 40 per cent of this loss is due to physical causes, i.e., pump and valve leakage, transfer losses

[49] Semon (to The B. F. Goodrich Co.), U. S. Pat. 2,366,360 (1945); *C. A.*, **39**, 2223 (1945).

[50] Smith and Braun, *Ind. Eng. Chem.*, **37**, 1047 (1945).

and incomplete separation from hydrocarbon streams.[40] As a result of improvements in the early operating techniques, however, recent estimates place the solvent loss at about 0.005 per cent.

When furfural is exposed to air, acidic conditions, certain organic sulfur or nitrogen compounds and to some unsaturated organic products such as butadiene, a certain amount of reaction occurs. If this reaction increases acidity, the rate of furfural decomposition will accelerate or, if temperatures rise too high, there will be increased solvent losses. Therefore, it is necessary to keep furfural streams relatively free from acids and dissolved oxygen.

Build-up of polymer in the furfural stream affects the selectivity and capacity of the solvent, hence polymer removal is also necessary. Experience has shown that this step need not be done each time furfural is used. It is sufficient to continuously withdraw 1–2 per cent of the circulating solvent and subject this to steam distillation to remove polymers and acids.[51, 52]

Mention has already been made that furfural plus about 4 per cent of water was a preferred solvent. Hachmuth has proposed a variation in which anhydrous furfural enters at the top of the tower, and as it passes down the column and absorbs butadiene and olefins, incremental amounts of water are added.[53] Arnold[54] states that furfural containing butenes has advantages over the pure solvent as an extractant for butadiene. Furfuryl alcohol is mentioned as a solvent for recovery of vinylacetylene.[42] Frey[55] has suggested a multiple stripping of the solvent. Since branched-chain olefins are more soluble in furfural than their straight chain isomers, it is possible to separate such mixtures by extractive distillation.[56]

Recovery of Aromatics from Catalytically Treated Petroleum Stocks. During World War II the demand for toluene exceeded the capacity of the coke industry and the petroleum industry was called upon to fill part of the demand. By catalytic dehydrogenation of selected petroleum fractions rich in naphthenes, a product with about 40 per cent toluene can be obtained.

[51] Hachmuth (to Phillips Petroleum Co.), U. S. Pat. 2,350,609 (1944); *C. A.*, **38**, 4962 (1944).

[52] Hachmuth (to Phillips Petroleum Co.), U. S. Pat. 2,372,668 (1945); *C. A.*, **40**, 718 (1946).

[53] Hachmuth (to Phillips Petroleum Co.), U. S. Pat. 2,411,785 (1946); *C. A.*, **41**, 855 (1947).

[54] Arnold (to Phillips Petroleum Co.), U. S. Pat. 2,379,332 (1945); *C. A.*, **40**, 588 (1946).

[55] Frey (to Phillips Petroleum Co.), U. S. Pat. 2,371,817 (1945); *C. A.*, **39**, 3539 (1945).

[56] Welling (to Phillips Petroleum Co.), U. S. Pat. 2,386,523 (1945); *C. A.*, **40**, 454 (1946).

The first commercial plant for the recovery of nitration-grade toluene from the above product was put into operation in 1940 at the Houston refinery of Shell Oil Co., Inc. The process involved extractive distillation, with phenol as the solvent. Because of the lack of time, it was not possible to conduct a complete survey of the relative merits of the numerous solvents considered for this application. Actual laboratory data indicated that on the basis of relative volatility, furfural was superior to the other solvents, and possessed the other characteristics desirable in an extractive agent.

However, in the absence of liquid-vapor equilibria data for systems of furfural and the non-aromatic components of the hydroformate, it was postulated that azeotrope formation in these systems was possible. Accordingly, it was decided to employ phenol as the extractive medium.

Recent liquid-vapor equilibria data on numerous furfural-hydrocarbon systems[56a] indicate little, if any, tendency for azeotrope formation and where the possibility exists, furfural is present in such small amount as to present little difficulty in its removal.

The increased need for benzene, coupled with the development of the platforming process, has aroused increased interest in aromatic production from petroleum, and has stimulated research on various techniques for aromatic recovery from the products of this process. Where the emphasis is on benzene production and recovery, the equilibria data indicate that furfural is well suited for this application. The use of furfural in extractive distillation of aromatics is under active consideration.

Refining Vegetable and Animal Oils

In retrospect, it seems strange that after the adoption of furfural as a refining agent for rosin and mineral oils, so many years elapsed before a similar process was applied to animal and vegetable oils. These latter are composed of saturated and unsaturated glycerides, free fatty acids, sterols, phosphatides, color bodies, and sometimes vitamins.

In 1937, a patent was issued in this field, which dealt primarily with the removal of malodorous and unpalatable constituents from oils containing vitamins A and D.[57] The process involved extraction with furfural in the cold, and it was suggested that a hexane solution of the oil be used in order to decrease the solubility of the oil and the vitamin fractions in furfural.

As the demand for special purpose oils for industrial and food uses increased, attention was given to the feasibility of modifying soya and lin-

[56a] Rae, H. K., Dissertation, Princeton University, 1950.

[57] Tischer (to Eastman Kodak Co.), U. S. Pat. 2,090,738 (1937); *C. A.*, **31**, 7278 (1937).

seed oils. Freeman[58] discusses the "treatment of glyceride oils such as linseed, oiticica, tung, soya, cottonseed, hemp seed, fish and tallow oils, among others, which are employed as film-forming constituents in paints, varnishes and enamels, and as food and drug products, and in soaps, plastics, etc." He points out that "above 104–106°F." furfural is an excellent solvent (even in 1:1 ratio) for free fatty acids, glycerides and color bodies normally present in oil-bearing seeds; that it is a relatively poor solvent for phosphatides. Thus, extraction of the seed with hot furfural separates glycerides from phosphatides. On cooling, the saturated glycerides separate from the extract phase leaving in solution, drying oil fractions, free fatty acids, color bodies and sterols. Addition of water to this solution throws down the unsaturated glycerides. Among other related patented disclosures the reader may wish to refer to Freeman,[59, 60] Beach and Robinson[61] and Jenkins.[62, 63]

By extraction with furfural, glyceride oils can be separated readily into a raffinate of relatively low iodine number, and an extract of high iodine number. In this separation, any natural antioxidants in the charge oil may be removed along with the extract, so that in some instances the drying rate of the extract may be slower than that of the original oil. When natural antioxidants are present, they can be removed from the oil by a preliminary "light" furfural extraction prior to the final exhaustive extraction with furfural to produce products of low and high iodine numbers. An alternative procedure involves the use of an additional solvent, naphtha, in the process illustrated in Figure 5.[64] The over-all effect of this procedure is to concentrate the antioxidants in the oil fraction of lowest iodine number.

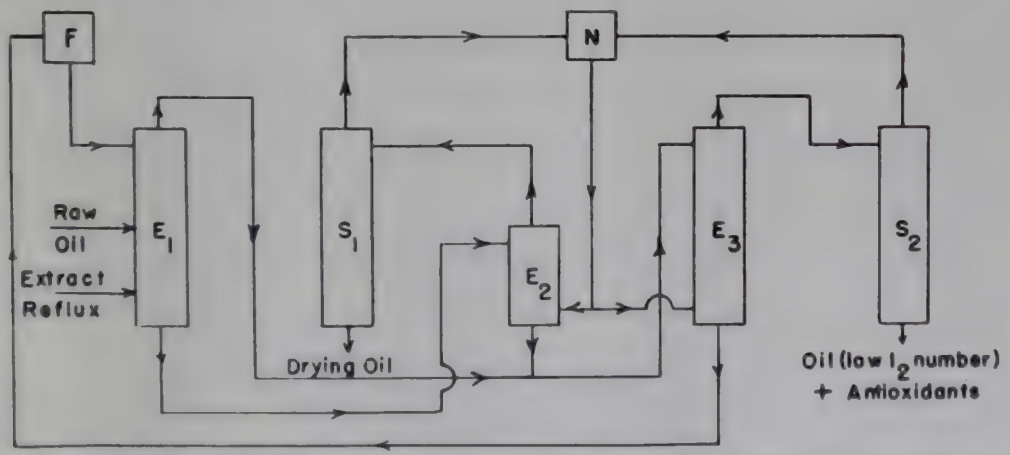


Figure 5. Flow Chart of Vegetable Oil Selective Solvent Refining
F—Furfural storage
N—Naphtha storage
E—Extractors
S—Stripping columns

[58] Freeman (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,200,390 (1940); *C. A.*, **34**, 6116 (1940).

[59] Freeman (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,200,391 (1940); *C. A.*, **34**, 6115 (1940).

Raw oil is countercurrently extracted with furfural in E_1. The raffinate comprising some furfural but, largely, oil fractions of low iodine number, is substantially free from antioxidants and is fed to E_3 where it is extracted with naphtha. The naphtha phase, containing oil but no furfural, passes overhead to S_2 where the naphtha is stripped from the oil and returned to storage.

The extract, or bottoms, from E_1 is a furfural solution of oil fractions of relatively high iodine number together with the natural antioxidants. It is given a light naphtha treatment in E_2, wherein the naphtha extracts the major portion of the oil leaving the antioxidants in the furfural phase. That is, the overhead from E_2 is substantially free of antioxidants but contains oil of high iodine number. This oil is freed of naphtha in S_1. The bottoms from E_2, consisting largely of furfural together with a small amount of oil of high iodine value, contains most of the antioxidants originally present in the charge oil. These bottoms are combined with the overhead from E_1 and are extracted with naphtha in E_3, a relatively large column because it is necessary to employ a very high ratio of naphtha to furfural in order to strip most of the antioxidants from the furfural. The overhead from E_3 is fed to S_2. The bottoms from E_3 consisting mainly of furfural with smaller amounts of oil and antioxidants, is recycled to E_1.

The operation of plants of this type involves all the techniques which were discussed in the sections on rosin and lubricating oil refining. However, in the case of vegetable oils, there is the additional factor that there may be little or no by-product. From an economic standpoint, the raffinate oil and the extract oil may be of the same value. Generally speaking, the oils of low iodine number may be used for food purposes; the more unsaturated oils find their way into resins, paints and varnishes. There is the distinct probability that some by-products, such as antioxidants and sterols, will be actively sought because, on a unit weight basis, they would be far more valuable than the oils themselves. By careful control of solvent ratios, temperature of extraction, size and arrangement of extraction towers, and reflux ratios, the desired degree of separation readily may be obtained.

The effect of many of these factors are discussed by Gloyer[65] (see also [66]), some of whose data have been compiled in Table 14. It will be apparent

[60] Freeman (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,313,636 (1943); *C. A.*, **37**, 5266 (1943).

[61] Beach and Robinson (to National Oil Products Co.), U. S. Pat. 2,265,020 (1942); *C. A.*, **36**, 1797 (1942).

[62] Jenkins (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,320,738 (1943); *C. A.*, **37**, 6921 (1943).

[63] Jenkins (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,352,546 (1944); *C. A.*, **38**, 5682 (1944).

[64] Ruthruff and Wilcox (to The Sherwin-Williams Co.), U. S. Pat. 2,355,605 (1944); *C. A.*, **39**, 204 (1945).

[65] Gloyer, *Ind. Eng. Chem.*, **40**, 228 (1948).

[66] Kenyon, Gloyer and Georgian, *Ind. Eng. Chem.*, **40**, 1162 (1948).

that the volume and iodine number of the raffinate both decrease as the ratio of furfural to charge oil is increased. The effect of tower height on yield and selectivity is shown by comparison of lines 3 and 4 of Table 14. In the shorter tower, less oil dissolves in the furfural which increases the yield of raffinate, but simultaneously decreases the selectivity. The data in lines 4, 5 and 6 are not strictly comparable, but indicate that selectivity in the 2-inch diameter column is considerably greater than in either the 22- or 66-inch diameter columns, even though these latter are of greater length.

TABLE 14. TREATMENT OF ALKALI-REFINED LINSEED OIL UNDER VARIOUS CONDITIONS[65]

Column Size	Furfural/feed oil ratio	Reflux ratio*	Raffinate		Extract		Difference in iodine numbers	Iodine number of feed oil
			Yield (vol. %)	Iodine number	Yield (vol. %)	Iodine number		
67′ x 66″	6.0	0.6	25.0	132.2	75.0	196.3	64.1	180.1
87′ x 22″	6.0	0.6	24.5	128.6	75.7	196.1	64.5	179.5
87′ x 22″	7.3	0.73	21.5	121.7	78.5	195.6	73.9	179.5
64′ x 22″	7.3	0.73	23.5	129.0	76.5	195.2	65.2	179.5
50′ x 2″	7.3	0.73	15.6	115.8	84.4	196.7	80.9	184.3
78′ x 66″	7.3	0.73	24.0	130.2	76.0	195.8	65.6	180.1

* Extract product reflux to feed oil ratio.

Up to 1948 most of the commercial solvent refining was carried out with alkali treated linseed oil. Raw linseed oil may be used if two extraction towers are employed. Such a system is similar to that illustrated in Figure 5 using only units E_1, E_2 and S_1. Furfural is the extracting solvent in E_1, and naphtha is used in E_2. The data in Table 15[65] are listed in accordance with this abbreviated system.

TABLE 15. TWO-TOWER EXTRACTION OF RAW LINSEED OIL[65]

Feed to E_1: 1 volume linseed oil containing 0.066 volume of naphtha.
6 volumes of furfural.
0.66 volume of extract product reflux.

Feed to E_2: extract product.
4 volumes of naphtha.

	Volume (%)	Iodine number	Free fatty acid (%)	Color (Gardner)
Raw oil		173.5	2.7	9.5
Drying oil (S_1)	59.6	196.5	0.5	7.5
Overhead (E_1)	37.3	141.3	0.6	8.0
Bottoms (E_2)	3.1	177.0	24.0	black

If crude soya oil is substituted for linseed oil, it is possible to produce a varnish grade oil without further refining. In this instance, the bottoms from E_2 contains sterols, tocopherols and free fatty acids. A sample of such a product containing 7.8 per cent of unsaponifiable material yielded 2.7 per cent tocopherol and 2.4 per cent sterol.

Table 16[65] (see also [67]) is similar to Table 14 except that it lists data for non-break soya oil instead of linseed oil. As before, a separation is made into relatively high and low iodine number fractions. However, if the overhead from the furfural extraction tower is fed to the lower section of a

TABLE 16. TREATMENT OF NON-BREAK SOYA OIL UNDER VARIOUS CONDITIONS[65]

Column size	Furfural/feed oil ratio	Reflux ratio*	Raffinate		Extract		Iodine number of feed oil
			Yield (vol. %)	Iodine number	Yield (vol. %)	Iodine number	
67′ x 66″	11.1	1.56	40.0	117.5	60.0	151.5	138.0
64′ x 2″	8.3	1.1	42.2	112.3	57.8	152.8	135.8
87′ x 2″	8.3	1.1	37.2	108.2	62.8	152.1	135.8
87′ x 2″	14.0	2.2	30.0	95.5	70.0	153.2	135.8

* Extract product reflux to feed oil ratio.

second furfural tower, it is possible to effect separation of the feed oil into three fractions, (1) an extract from the bottom of the first column, (2) an intermediate extract from the bottom of the second tower, and (3) a highly refined oil from the overhead of the second tower. Treatment of non-break soya oil in this manner gave the data listed in Table 17.[65] The extract from

TABLE 17. TWO-TOWER FURFURAL EXTRACTION OF NON-BREAK SOYA OIL[65]

Feed to column 1: 1 volume charge oil.
6 volumes furfural.
0.88 volume extract reflux.

Feed to column 2: overhead from column 1.
3.75 volumes furfural.

	Volume (%)	Iodine Number
Charge oil		135
Extract, column 1	25	160
Extract, column 2	50	134
Raffinate, column 2	25	105

[67] Gloyer, *J. Am. Oil Chemists' Soc.*, **26**, 162 (1949).

the second column is suitable for winterized salad oil and the raffinate is satisfactory for hydrogenation. Further treatment of the first extract with naphtha gives a varnish oil fraction.

By a combination of furfural and naphtha extractions, the vitamin A potency of dogfish liver oil has been increased about five-fold.[65] The method is the same as described previously for the two-tower extraction of linseed oil (see Table 15), and again referring to Figure 5, the essential units of equipment are E_1, E_2, and S_1. Furfural, saturated with naphtha, is the extractant in E_1; naphtha in E_2. The vitamin A is concentrated in the furfural from which it is subsequently extracted by naphtha in E_2. The data obtained in this operation are listed in Table 18. By changing the solvent/oil ratios, potencies as high as 150,000 I.U. of vitamin A per gram

TABLE 18. TWO-TOWER EXTRACTION OF DOGFISH LIVER OIL[65]

Feed to column E_1: 1 volume dogfish liver oil.
20 volumes furfural saturated with naphtha.
0.36 volume naphtha reflux.
0.17 volume extract reflux.

Feed to column E_2: extract from column E_1.
15 volumes naphtha.

	Volume (%)	Iodine number	Vitamin A	
			% of original	Potency (I.U./gram)
Charge oil		109	100	17,000
Vitamin oil, from S_1	19.1	173.8	89.5	82,000
Overhead from E_1	78.4	90.2	5.3	1,200
Bottoms from E_2	2.5	161.2	0.9	6,600

have been obtained. The flavor of the high potency oil was observed to be much improved over that of the original oil and despite the relatively high iodine number of its carrier, the potency remained constant for eight months.

The application of solvent refining to fish liver oils encounters serious difficulty because of the relatively limited quantities of such oils and, to some extent, because of the seasonal nature of the fishing industry. Fish body oils are obtained in much larger quantities, and the solvent process might be practical for such oils. Vegetable oils such as corn, soya, and linseed oils are available the year round in large volumes, and it is with these that solvent refining is most likely to achieve industrial success.

Purification of Tall Oil and Sulfate Turpentine

Tall oil and sulfate turpentine are malodorous, dark-colored by-products from the manufacture of kraft or sulfate pulp. The former consists of from 25 to 60 per cent of fatty acids (mainly of the oleic and linoleic series), 25 to 60 per cent of rosin acids (largely abietic) and from 2 to 7 per cent of lignin, mercaptans, phytosterols, higher alcohols and waxes. The color bodies are similar to those in furfural-grade wood rosin and the odorous compounds are sulfur and nitrogen compounds which are readily soluble in furfural. These facts suggest that tall oil could be refined, both as to color and odor, by extraction with furfural. Two such processes have been developed, although neither has been used commercially to date, presumably because tall oil and wood turpentine are mostly produced in relatively small quantities (2,000 gallons per day or less), which are not large enough to justify the expense of installing selective solvent refining equipment.

In one of the processes,[68, 69] tall oil is partially purified and then dissolved in gasoline. The solution is filtered and extracted with 25 to 50 volume per cent of furfural at 50°. On cooling, the upper phase comprising a gasoline solution of tall oil, is separated from the lower, furfural layer.

The second process is due to Trimble,[70] who describes a method for refining sulfate turpentine with furfural. More interesting, however, is his observation that if crude tall oil and sulfate turpentine are mixed and subjected to countercurrent extraction with furfural, both crude products are purified simultaneously and may be separated by vacuum distillation. Esters of the rosin acids of tall oil may likewise be purified with furfural, furfuryl alcohol or methylfuran, according to another patent.[71]

Recovery of Acetic Acid from Aqueous Solution

Three methods involving the use of furfural have been proposed for recovering acetic acid from aqueous solutions. For example, activated carbon preferentially adsorbs acetic acid from dilute aqueous solution,[72] following which the acid can be extracted from the carbon by furfural, and recovered by fractional distillation.

Another method uses furfural as a water entraining agent. This takes advantage of the fact that the constant boiling mixture of furfural and water contains 65 per cent water and 35 per cent furfural. Furthermore,

[68] Blengsli, *Paper Trade J.*, **111**, No. 10, 37 (1940).

[69] Blengsli, U. S. Pat. 2,111,259 (1938); *C. A.*, **32**, 3992 (1938).

[70] Trimble (to The Quaker Oats Co.), U. S. Pat. 2,310,046 (1943); *C. A.*, **37**, 4265 (1943).

[71] Freeman and Gloyer (to Pittsburgh Plate Glass Co.), U. S. Pat. 2,423,232 (1947); *C. A.*, **41**, 6048 (1947).

[72] Spence (to Masonite Corp.), U. S. Pat. 2,422,504 (1947); *C. A.*, **41**, 5893 (1947).

this azeotrope, boiling at 97.90°, lowers the concentration of acetic acid in the vapor which is in equilibrium with the acid-water solution.[73]

The third method is based on direct liquid-liquid extraction. The distribution of acetic acid between furfural and water is about 1 to 1, and in an efficient countercurrent extraction operation employing two volumes of furfural to one volume of aqueous feed containing as much as 30 per cent acetic acid, the acid content of the aqueous effluent can be reduced to about 0.1 per cent. Pilot plant demonstrations have shown that recovery is practical from aqueous solutions containing as little as one per cent acetic acid.

A flow diagram of one form of this process is shown in Figure 6.[74] Dilute acid enters near the bottom of extraction tower A, where it meets a descending stream of furfural. As the aqueous solution rises, the acid is extracted by the furfural. The height of the tower and ratio of furfural to feed are so adjusted that the effluent from the top of A contains only 0.1 to 0.2 per cent acid and 7 to 9 per cent furfural. This effluent is sent to column B where the furfural is removed as the constant boiling furfural-water azeotrope which is condensed and collected as two layers in a decanter. The upper, aqueous layer is returned as reflux to B and the lower, wet furfural is used as reflux for column C. The bottoms from B, which is discarded, contains all of the water originally present in the feed together with what little acid was not stripped from the feed by the furfural.

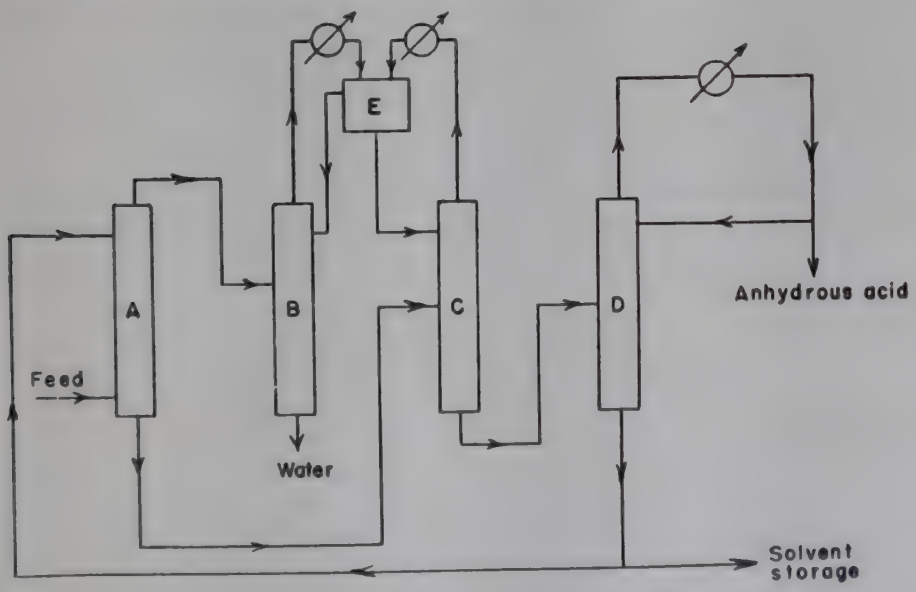


Figure 6. Recovery of Acetic Acid from Aqueous Solution
A—Extractor
B—Furfural stripper
C—Azeotropic column
D—Furfural-acid column
E—Decanter

[73] Wentworth, U. S. Pat. 2,123,348 (1938); *C. A.*, **32**, 6672 (1938).
[74] Wentworth, U. S. Pat. 2,255,235 (1942); *C. A.*, **36**, 99 (1942).

The bottoms stream from A is furfural containing about 5 per cent water and 5 per cent or more acetic acid; the acid concentration depends on the ratio of solvent to feed, the efficiency of the extractor, and the temperature. This ternary mixture is fed to the middle section of azeotropic column C. Water-furfural vapor passes overhead, is condensed and collected in the decanter. The furfural-acetic acid solution from the bottom of C is practically anhydrous. This is fed to column D where the components are separated by ordinary fractionation, preferably under vacuum.

This process would work equally well with homologs of acetic acid such as formic or propionic. If more than one acid is present, a mixture is recovered from column D, which can be fractionated in an additional column.

It is almost certain this latter method is practical from an operating viewpoint, but no commercial unit has been installed. Where the concentration of acetic acid in the charge stock is low, a relatively high capital investment is required and in at least two cases this was the factor which prevented construction of a plant.

Purification of Anthracene

Chronologically, the second commercial application of furfural as a refining agent was to separate anthracene from crude anthracene oil, consisting largely of anthracene, carbazole, and phenanthrene. During 1928, substantial quantities of furfural were used for this purpose,[74a] although the process has not been in use since 1930. As such, it is the only large scale furfural solvent refining operation which, once established, has been discontinued.

As practiced, the process involved dissolving the crude material (*ca.* 30 per cent anthracene) in the minimum quantity of furfural required to effect solution at 80°. On subsequent cooling (15–20°), 95 per cent of the anthracene crystallizes out in purity somewhat in excess of 80 per cent. Where desired, the operation may be repeated with fresh furfural to attain yet higher purity.

Miscellaneous Solvent Uses

Industrial Coatings

Furfural and furfuryl alcohol are excellent solvents for many coating resins and are generally compatible with other ingredients of coating compositions. Despite the great volume of literature on the subject, however, comparatively little of these products is sold for use in this field. There are a number of reasons for this, among which are color, odor, and, possibly in former years, price. Probably color has been the greatest handicap, al-

[74a] Jaeger (to Selden Research & Engineer), U. S. Pat. 1,693,713 (1929); *C. A.*, **23**, 851 (1929) [Reissue 17,902 (1931)]; Jaeger and Daniels (to Selden Co.), U. S. Pat. 1,841,895 (1932); *C. A.*, **26**, 1759 (1932), 1,892,770–2 (1933); *C. A.*, **27**, 1642, 2158 (1933).

though tests have shown that there is very little pigment in even very dark-colored samples of furfural and furfuryl alcohol, so that it is possible to use them in all but the lightest colored or clear lacquers. With reference to odor, furfuryl alcohol presents no problem, but opinion differs in the case of furfural. Thus, some years ago, a nationally known consultant wrote in a paint journal, "The odor of liquid furfural is pleasant, resembling almond oil," whereas another authority is quoted, two years later, as having said, "It (furfural) has a very disagreeable odor, which persists for a long time (in lacquer films)."

Many patents and articles describe furan derivatives, including furfural, furfuryl alcohol and tetrahydrofurfuryl alcohol as solvents for nitrocellulose, cellulose acetate and other cellulose derivatives (see, for example [75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85]). Aliphatic esters of furoic acid are excellent high-boiling solvents for many gums and cellulose esters,[82] and limited commercial use of these was fairly common in years past. Because there was no large scale production of furoic acid, the esters were relatively expensive and they have not been available for a number of years.

At the present time, a wire-coating application is practiced in the United States and Canada which utilizes furfural as a high-boiling solvent for cellulose acetate. This use was patented in the 'thirties[86, 87] when commercial furfural was of poorer quality than current production, and when a resinous impurity in the furfural appears to have been instrumental in converting the cellulose acetate coating into a more flexible, insoluble film with better adhesion to the wire. In recent years, new interest in this application revealed the desirability of this resinous impurity, and necessitated the development of practical means for introducing it into the relatively pure furfural now available. This involved deliberate partial autoxidation of the furfural which, as discussed earlier (p. 385), forms products subject to polymerization on standing.

[75] Meunier, French Pat. 472,423 (1913).

[76] Chem. Fabrik von Heyden Akt.-Ges., German Pat. 302,460 (1917); *C. A.*, **15**, 177 (1921).

[77] Bonwitt, British Pat. 138,078 (1920); *C. A.*, **14**, 1762 (1920).

[78] Steimmig, German Pat. 307,075 (1919).

[79] Carroll, U. S. Pat. 1,450,716 (1923); *C. A.*, **17**, 1887 (1923).

[80] Trickey (to The Quaker Oats Co.), U. S. Pat. 1,703,697 (1929); *C. A.*, **23**, 2050 (1929).

[81] Trickey (to The Quaker Oats Co.), U. S. Pat. 1,756,228 (1930); *C. A.*, **24**, 3122 (1930).

[82] Trickey, *Ind. Eng. Chem.*, **19**, 643 (1927).

[83] Gardner, *Paint Mfrs. Assoc. of U. S.*, Circ. **209**, 67 (1924).

[84] Leit, *Kunstoffe*, **16**, 241 (1926).

[85] Light, *Paint Varnish Production Mgr.*, **13**, 18 (July, 1935).

[86] Converse (to Case, Pomeroy & Co.), U. S. Pat. 2,059,441 (1937); *C. A.*, **31**, 481 (1937).

[87] Converse (to James K. Delano), U. S. Pat. 2,118,838 (1938); *C. A.*, **32**, 5536 (1938).

As a solvent for polyvinylformal, furfural was used in the development of Formex insulating wire.[88] In many applications of copper insulating wire, as in the production of random-wound coils, it is necessary that the coating be hard and flexible, and resistant to abrasion and to the softening effect of solvents when the coil is impregnated with insulating varnish. To meet these requirements, the General Electric Company developed a wire enamel which comprises polyvinylformal together with a thermosetting phenolic resin in suitable solvent medium. Economic considerations generally govern the composition of the solvent medium, both furfural and crude tar acids being applicable, either alone or in admixture in proportions dictated primarily by relative cost.

Furfural is also used in small amounts as a component (15–30 per cent) of the solvent carrier for insulating varnishes based on tung oil-modified phenolic resins. Other applications have been in connection with the formulation of baking varnishes for coating tin and aluminum, and in the preparation of certain metal-metal adhesives from epichlorohydrin resins.

During World War II, furfuryl alcohol was substituted for anhydrous, denatured alcohol as a solvent for the dichromated gum arabic coating used in the preparation of deep-etched aluminum lithograph plates. Only one-fourth as much furfuryl alcohol is required compared to the more commonly used alcohol, so that relative costs are about equal. "Practical tests have shown furfuryl alcohol is at least as satisfactory, and possibly more so than anhydrous, denatured alcohol for this purpose".[89]

Tetrahydrofurfuryl alcohol is essentially colorless, and is stable in storage. It is a good solvent for varnish, lacquer and enamel ingredients, and as a lacquer solvent (see [80, 90]), is reported to have a high (7.8) toluene-dilution ratio. Its price has militated against large-scale use as a coating solvent, although certain specialty applications have been developed, where other, less costly solvents failed to accomplish the desired results. Of mild, pleasant odor, tetrahydrofurfuryl alcohol has sufficiently low volatility to permit its use with ordinary mineral spirits. It does not reduce the natural gloss of coatings, and it improves their brushability even when present in relatively small amount. This desirable combination of properties is difficult or impossible to achieve with any other alcohol. As a solvent for cellulose acetate, tetrahydrofurfuryl alcohol is used in the preparation of adhesive for decalcomania transfers. Handling of the decals is simplified by the slow rate of evaporation of the solvent, but equally important in this application is the

[88] Hall (to General Electric Co.), U. S. Pat. 2,114,877 (1938); *C. A.*, **32,** 4690 (1938).

[89] Reed and George, "Furfuryl Alcohol in Deep-Etch Plate Making," Lithographic Technical Foundation, Inc., *Research Bulletin No. 9*, Suppl. No. 3, 2 pp., New York (1942).

[90] Bradshaw (to E. I. du Pont de Nemours & Co.), British Pat. 279,520 (1926); *C. A.*, **22,** 3056 (1928).

solubility of the alcohol in water, since this permits some dilution of the adhesive composition with water.

In the production of hectograph films, tetrahydrofurfuryl alcohol has found application in connection with gelatin mats. Added to the extent of a few per cent, it acts to promote adhesion to the base or backing material. To a lesser extent, furfuryl alcohol has also been used for this purpose, but unlike its saturated relative, it appears to effect some undesirable hardening action on the gelatin.

The solubility of a number of commercially available thermoplastic resins in furfural, furfuryl alcohol and tetrahydrofurfuryl alcohol has been determined in a semi-quantitative manner, as indicated by the data in Table 19. In a few instances there was evidence of fractional solubility (e.g., vinyl acetate, vinyl acetate-chloride, and methyl methacrylate, HM-122 in furfural). At about ten per cent concentration, vinylbutyral in furfural, and vinyl acetate-chloride in tetrahydrofurfuryl alcohol formed gel-like mixtures at room temperature, but were transformed into true solutions on heating and remained so on subsequent cooling.

Dye Solvents

Furfuryl alcohol has been found to be a solvent for a number of difficultly soluble dyes, and is regularly employed by silk screen printers to dissolve leuco vat ester salts. Specific dyes which are soluble in the alcohol are Indigosol Golden Yellow (IGK and IRK), and Indigosol Brown (IRRD). Cotton textiles are also printed with furfuryl alcohol dye solutions.[91a]

The use of furfural as a dye solvent is limited by its reactivity. A number of years ago it was employed rather extensively as a solvent for nigrosine in the manufacture of shoe dye, but this outlet no longer exists.

Sludge Removers

For the past twenty years, some owners of bus and taxicab fleets have used furfural, alone or in admixture with a tar-acid oil, for flushing the crankcase as a regular engine-maintenance operation. This treatment keeps the piston rings and grooves, and the crankcase free from sludge and "varnish" and generally improves the compression. At the present time, taxi fleets in New York City and in Chicago are so treated. After draining the lubricating oil, the furfural mixture is added, and the motor is run for 10 to 30 minutes at a fast idling speed. The crankcase is drained, flushing oil is introduced to remove the last traces of the solvent mixture, and after draining, fresh lubricating oil is added and the engine is ready for operation.

[91] The Quaker Oats Company, unpublished data.

[91a] Durand & Huguenin S. A., French Pat. 769,171 (1934); *C. A.*, **29**, 619 (1935).

TABLE 19. SOLUBILITY OF SOME THERMOPLASTIC RESINS IN FURAN COMPOUNDS[91]

(Room temperature except where indicated)
S = soluble in the range 1–10 g. per 100 g. of solvent
VS = soluble to extent of 10 g. or more per 100 g. solvent
I = insoluble, or less than *ca.* 1% soluble

Resin	Manufacturer (Code No.)	Solubility		
		Furfural	Furfuryl alcohol	Tetrahydrofurfuryl alcohol
Cellulose nitrate	Hercules	VS	VS	VS
Ethylcellulose	Hercules (N-50)	VS	VS	VS
Cellulose acetate	Hercules (PM-3)	VS	VS	VS
Cellulose acetate-butyrate	Tennessee-Eastman (AB-500-1)	VS	VS	VS
Vinylbutyral	Bakelite (XYHL)	S; VS (hot)	VS	VS
Vinyl acetate	Bakelite (AYAT)	S (hot)*	VS	VS
Vinyl acetate-chloride	Bakelite (VYNH)	S (hot)*	I	VS
Vinyl acetate-chloride	Bakelite (VYNS)	S (hot)*	I	S; VS (hot)
Vinyl chloride	Martin (VR-10)	I	I	I
Vinyl-vinylidene chloride	Goodrich (Geon 205)	S (hot)	I	S (hot)
Nylon	Dupont (FM-3001)	I*	I	I
Nylon	Dupont (FM-6501)	I*	VS†	I
Nylon	Dupont (FM-7001)	I*	I	I
Methyl methacrylate	Dupont (HM-122)	S (hot)*	VS	I
Methyl methacrylate	Dupont (HM-130)	VS	VS	S (hot)
Polyethylene	Dupont (PM-1)	I*	I	I
Styrene	Dow (PS-3)	S (hot)	I	VS

* Cloudy † Slow

With badly sludged motors, it is generally more economical to treat the engine with flushing oil prior to the furfural treatment.

A somewhat similar treatment has been inadvertently applied to a good many stationary gasoline engines when the maintenance man added furfural in the mistaken idea that it was lubricating oil. In one instance, a rather large engine driving a compressor was in operation for about a week with nothing but furfural in the crankcase. Although this practice is not to be recommended, no damage resulted, and the engineer reported that the engine had better compression after the extended exposure to furfural than before.

Another application in the automotive field involves the use of furfuryl alcohol as a solvent or "loosening agent" for carbonaceous deposits in the combustion chambers of internal combustion engines. Operation of the engine is stopped, and furfuryl alcohol, in admixture with other solvents, is injected into the cylinders and allowed to remain there for several hours. This treatment loosens contaminating deposits by softening or dissolving the gummy binder, and when the engine is started, the deposit is removed with the exhaust gases.[92] A carbon remover of this type, Remo, was optional equipment on Oldsmobile cars in the early 'thirties. It was very effective whenever fresh solvent was used, but when the solution was carried under the hood for long periods of time, polymerization progressed to the point where the product had lost its power to loosen carbon deposits.

Furfural is an excellent solvent for the undesirable deposits encountered in the lines, valves, and other equipment of manufacturers and distributors of artificial gas. Such deposits reduce efficiency of operation, and in severe cases may lead to plugging of lines. The use of furfural to minimize difficulties of this nature has been carried on for many years, particularly in the eastern states.

Paint and Varnish Removers

Furfural and furfuryl alcohol have received a good deal of attention as components of paint and varnish removers because of their solvent properties and low volatility. The latter is an important consideration in applications of this type. For example, the use of low-boiling solvents generally necessitates the incorporation of wax or other agent to retard evaporation, and this practice has the disadvantage of decreasing the cutting power of the remover, and of leaving a wax-film on the treated surface which complicates refinishing. Pollak[93] has discussed the advantages of using furfural as a component of paint removers, calling particular attention to the fact

[92] Lovell and Boyd (to General Motors Research Corp.), U. S. Pat. 1,820,395 (1931); *C. A.*, **25**, 5754 (1931).

[93] Pollak, *Paint, Oil Chem. Rev.*, **109**, No. 15, 9 (1946).

that solvent combinations containing furfural "cut" faster than any one of the components when used alone. He recommends a mixture of acetone and furfural as a practical remover, and stresses the low toxicity of such a combination.

A major application of furfural is found in the formulation of industrial stripping baths for removing a variety of coatings. For example, a mixture of furfural (one part) and perchloroethylene (two parts) is currently being used for stripping (*ca.* 130°F.) many types of finishes, including oleoresinous varnishes and baked alkyd coatings. Solvent losses due to evaporation are minimized by providing a supernatant water layer, and the bath is occasionally treated with sodium bicarbonate in order to neutralize acidic degradation products having their origin in the chlorinated hydrocarbon. It is reported that baked vinyl finishes are not particularly susceptible to removal in this manner.

Also of interest is the use of furfural for removing ink mill-markings from sheet metal. In certain instances, tempering rolls may pick up these markings and reprint them repeatedly as sheet metal is run through the rolls. Furfural quickly and easily removes the markings and thereby eliminates this difficulty.

In Urea Adhesives

Furfuryl alcohol is used in the manufacture of gap-filling and craze-resistant adhesives from urea-formaldehyde resins.[94] Where the glue line is heavy, as in cementing together rough surfaces, unmodified urea adhesives are subject to cracking, and poor adhesion on aging. By incorporating furfuryl alcohol in such compositions, the adhesive becomes resistant to crazing, and has improved flexibility and a faster rate of cure. The dimensional stability of the adhesive is also improved. Thus, a casting of the furfuryl alcohol-modified adhesive has been observed to retain its shape, with no crazing, even after subjection to a temperature of 176°F., for 24 hours. This desirable combination of properties, not possessed by unmodified urea resins, makes the furfurylated adhesives useful in bonding phenolic-base paper laminates, decorative laminates, hardboard, lumber core gluing, edge-bonding of furniture, wood to wood joint gluing and in abrasive binding.

In formulating these modified adhesive compositions, storage-stability is achieved by heating the furfuryl alcohol-urea resin mixture for a short time under mildly alkaline conditions. At time of use, the adhesive is catalyzed in the manner normally used with ordinary urea glues to attain the desired relationship between rate of cure and working-life. These commercially available adhesives exceed the minimum property requirements

[94] Simons (to American Cyanamid Co.), U. S. Pat. 2,518,388 (1950).

of Army-Navy Aeronautical Specification Glue (Cold Setting Resins, AN-G-8 Specification), as well as Federal Adhesive Specification CG-496.

Cold-molding of Resin-Bonded Abrasive Wheels

Many years ago, Brock,[95] and later, Martin[96] found that the addition of a small amount of furfural to abrasive grain-resin mixtures produced mixes which could be cold-molded. Prior to this finding, the production of resin-bonded abrasive wheels was small because of the expense and the time-consuming nature of the hot-molding method. Since then, most resinoid wheels have been manufactured using furfural, which serves a two-fold function, (1) to wet the abrasive grains, and (2) to soften the powdered resin particles so that they cling to the abrasive. After thorough mixing, the coated grains are screened, charged into molds, cold molded, placed on porous plates, and cured in a hot air-circulating oven. Comparatively small amounts of furfural are effective, usually from 1–2 per cent of the total weight of the mix, or 10–20 per cent of the quantity of powdered resin. A typical mix for abrasive wheels has the following approximate composition:

aluminum oxide grains	87.5 lbs.
powdered phenolic resin	12.5 lbs.
furfural	1.75 lbs.

Frequently some form of humidity and temperature control is employed in the mixing room, because slight changes in the "wetness" of the mix may affect the properties of the finished wheels.[97]

The use of furfural in this application makes possible the uniform distribution of the resin on the abrasive grains. It also imparts an appreciable amount of cold flow under pressure during the brief molding cycle. Additionally, if there is an excess of phenol in the binding resin, furfural will react with it,[98] and will become an integral part of the final cured resin, thereby helping to produce a hard, shock-resistant resin bond. Some manufacturers deliberately add calcium oxide to the mix in order to promote reaction between furfural and the phenolic resin. Where hexamethylenetetramine is used as the cross-linking agent for the phenolic resin, the furfural can react with any liberated ammonia, and in this way, lessen the danger of delamination and formation of "blow-holes". During the late 'thirties, the statement was made that the use of furfural in the production of resin-bonded abrasive wheels had reduced costs incident to the rough-finishing of heavy motor castings to about one-fifth of the amount formerly

[95] Brock, U. S. Pat. 1,537,454 (1925); *C. A.*, **19**, 2116 (1925).
[96] Martin, U. S. Pat. 1,576,440 (1926); *C. A.*, **20**, 1499 (1926).
[97] Martin (to Carborundum Co., Ltd.), British Pat. 316,189 (1928); *C. A.*, **24**, 1717 (1930).
[98] Mills (to Bakelite Corp.), U. S. Pat. 2,008,723 (1935); *C. A.*, **29**, 6010 (1935).

charged to such operations. Toughness and resistance to shock, properties which are necessary in satisfactory snagging wheels, are characteristically present in wheels manufactured with the aid of furfural.

TABLE 20. REACTION OF FURFURAL AND FURFURYL ALCOHOL WITH PHENOLIC RESINS[91]

Phenolic resin	Furfural		Furfuryl Alcohol	
	Amt. added to resin (% by weight)	Retention in fully cured resin* (% of amt. added)	Amt. added to resin (% by weight)	Retention in fully cured resin* (% of amt. added)
"Bakelite" 0215	10	90	10	94
"Bakelite" 0215	20	87	20	86
"Bakelite" 2417	20	85	20	83
"Durez" 7031	20	88	20	85
"Durez" 8045	—	—	20	77
"Durez" 14000	—	—	20	87
"Durite" 278	10	96	10	91
"Durite" 278	20	96	20	92
"Durite" 3022	10	95	10	93
"Durite" 3022	20	92	20	89
"Durite" 1530	20	93	20	92
Monsanto 795	20	88	—	—
"Varcum" 1364	20	87	20	84
"Varcum" 1192 (syrup)	20	69	20	80

* The mixtures of furfural or furfuryl alcohol, and the resins were triturated and then baked in a shallow pan. The heating cycle was 80°C., for 3.75 hours, 100°C., for 24 hours. The samples were weighed before and after baking, and the yield of cured resin was compared to that obtained by similar baking of control samples of the various resins containing no furfural or furfuryl alcohol. That the gain in weight in the former instances was not due to occlusion of the furan compounds was demonstrated in two instances by powdering the cured samples and baking for an additional 8 hour period at 180°C., in a vacuum oven. Under these conditions, control samples of phenolic resin lost about 3% in weight, whereas the cured samples to which furfural or furfuryl alcohol had been added lost only about 1% in weight.

Furfuryl alcohol has many of the solvent, surface-active, and resin-forming characteristics of furfural, and several grinding wheel manufacturers prefer to use the alcohol in their operations. It is reported that it can be used in even lesser amounts than is furfural, although this is doubtful. If an advantage does exist, it probably lies in the production of a freer-flowing, and thus, more easily handled resin-abrasive mix. The use of furfuryl alcohol is also reported to eliminate the necessity for rigid control of humidity

and temperature.[99, 100] For the most part, however, furfural appears to be the preferred solvent and wetting agent for this application.

Furfural is also employed in other cold-molding processes involving the use of phenolic resins, including the production of brake-linings, clutch facings and particularly, brake-blocks. In general, the furfural is added as a wetting agent to the finely powdered fillers which comprise about 10–15 per cent of a typical brake lining mix. The rest of the mix includes 50–60 per cent of asbestos fiber and 20–25 per cent of phenolic resin. A similar application is concerned with the formulation of resin-bonded, asbestos-filled cold-molding compositions for manufacturing electrical parts.

In all of these applications, furfural is used to improve the uniformity and plasticity of the various mixes; to assist in the formation of a strong bond between the abrasive grain, the asbestos fiber or other filler, and the phenolic resin. The complete fulfillment of these functions by furfural, and by furfuryl alcohol is due at least partially to their excellent solvent and wetting characteristics. Possibly of no lesser importance, however, is the fact that very little of these solvents is lost by evaporation in the final curing operation. That is, they appear to become, in large measure, a part of the bonding resin as shown by the data in Table 20. In other words, furfural and furfuryl alcohol may be classified as reactive solvents when used with phenolic resins. Interesting and potentially useful applications of this property are currently under development in other industries.

[99] Novotny and Kuzmick, (one-half each to John S. Stokes and Raybestos-Manhattan, Inc.), U. S. Pat. 1,924,748 (1933); *C. A.*, **27**, 5505 (1933).

[100] Anon., *Brit. Plastics*, **5**, 546 (1934).

Chapter 18

FURFURAL AND FURFURYL ALCOHOL RESINS

The resin-forming propensity of furfural has been recognized for over a hundred years,[1, 2] but until the industrial value of phenol-formaldehyde resins was demonstrated, this property was of purely theoretical interest. By the time furfural was available in commercial quantities, however, phenolic resins had been industrially accepted, and the manufacture of phenol-furfural types was begun in the early 1920's. On the other hand, during the period of the most rapid development of the phenol-formaldehyde resins, the patents covering the use of furfural were closely held, and this militated against large scale use of furfural-phenolics. Although some specialty applications were developed, it was not until about 1945 that the use of furfural in resins began to expand rapidly. In the meantime, furfuryl alcohol had become commercially available, and its resin-forming properties were found to be at least as interesting as those of furfural. Thus, today, while the use of furfural-phenolics is still increasing, applications for furfuryl alcohol resins are growing at a much faster rate.

Up to the present time, approximately one thousand U. S. patents have been issued which deal with the production or use of various furan resins. The field is by no means exhausted, however, since there are almost limitless possibilities in new combinations, or specific reactants, which differ in some degree from anything heretofore suggested. This is particularly true in the furan field where, because of the polyfunctionality of furan compounds, apparently slight modifications of a few basic reactions may permit the "tailoring" of resins to fit a wide variety of specific property requirements. The following references may be of general interest to the reader: Peters,[3, 4] Novotny,[5] Barry and Light,[6] Light,[7] Penn,[8] Dunlop and Peters,[9] Farmer,[10]

[1] Stenhouse, *Ann.*, **35**, 301 (1840).
[2] Fownes, *Ann.*, **54**, 52 (1845).
[3] Peters, *Modern Plastics*, **13**, No. 11, 38 (1936).
[4] Peters, *Ind. Eng. Chem.*, **31**, 178 (1939).
[5] Novotny, *Modern Plastics*, **14**, No. 2, 33 (1936); **16**, 32, 154 (1938); **17**, No. 2, 55 (1939).
[6] Barry and Light, *Brit. Plastics*, **5**, 535 (1934).
[7] Light, *Brit. Plastics*, **11**, 314 (1939).
[8] Penn, *Brit. Plastics*, **16**, 286 (1944).
[9] Dunlop and Peters, in Alexander, "Colloid Chemistry," Vol. VI, New York, Reinhold Publishing Corp. (1946).
[10] Farmer, *Chem. Age*, **45**, 23 (1941).

Kline[11] and Norton.[12] Additionally, The Quaker Oats Company, Chemicals Department, has available in mimeographed form, abstracts of the majority of the patents which have been granted dealing with the preparation of furan resins and their applications. The index to these abstracts is appended to this chapter for the convenience of those interested.

Furfural-phenolic Resins

The phenolic resin industry is, by far, the largest consumer of the furfural which finds its way into resin applications. The term, phenolics, generally includes plastics and resins derived from aldehydes and phenolic compounds, the latter including phenol itself, cresol, xylenol, resorcinol, and related types. The complex condensation products obtained by placing furfural in reaction with cashew nut shell oil are also included here, inasmuch as the aldehyde-reactive constituents of the oil are phenolic in character.

Comparatively little is known with reference to the chemistry of the reaction of furfural with phenols (Chapter 9), and it is not unlikely that the structure of the final, completely cured resin is considerably more complex than that of the related phenol-formaldehyde resins. From the standpoint of the manufacturer, it is certainly true that, relative to the latter types, modified operating conditions must be employed in order to obtain useful resins from phenol and furfural. The most common phenol-formaldehyde resins are the two-stage, or novolac types, permanently fusible and soluble compositions which become thermosetting when compounded with hexamethylenetetramine. Production generally involves reacting formaldehyde with slightly more than one molecular equivalent of phenol in the presence of an acid catalyst. Under similar conditions, however, furfural and phenol frequently give rise to a worthless gel-like mass, although this can be overcome, and fusible resins have been obtained by employing a substantial excess of phenol.[13, 14, 15] Nevertheless, the acid-catalyzed reaction is difficult to control in the case of furfural, and interest shifted to the use of alkaline catalysts at a relatively early date.[16, 14, 17, 18, 19] In this way it is possible to

[11] Kline, National Bureau of Standards, Technical News Bulletin, "Plastics in Germany," Washington, D. C., October, 1945.

[12] Norton, *Ind. Eng. Chem.*, **40**, 236 (1948).

[13] Novotny and Kendall, U. S. Pat. 1,398,146 (1922); *C. A.*, **16**, 843 (1922).

[14] Beckman and Dehn, *Sitzb. kgl. preuss. Akad. Wiss.*, **1918**, 1201; *C. A.*, **14**, 642 (1920).

[15] Ellis, "Synthetic Resin and Their Plastics," p. 206, New York, Chemical Catalog Co., Inc. (Reinhold Publishing Corp.), 1923.

[16] Trickey, Miner and Brownlee, *Ind. Eng. Chem.*, **15**, 65 (1923).

[17] Novotny and Kendall (to John S. Stokes), U. S. Pat. 1,705,495 (1929); *C. A.*, **23**, 2309 (1929).

[18] Miller (to Bakelite Corp.), U. S. Pat. 1,717,614 (1929); *C. A.*, **23**, 4090 (1929).

prepare phenol-furfural resins with properties rather closely akin to those of the phenol-formaldehyde novolacs except that, unlike the latter, the furfural resins are not permanently fusible. The procedure involves reacting furfural (1 mole) with phenol (1.2 to 3.0 moles) under closely controlled conditions. The unreacted phenol is removed during the dehydration step, care being exercised to accomplish this as rapidly as possible, and to avoid excessive temperatures which might otherwise advance the resin beyond the usable stage. Resins prepared in this general manner are the furfural-phenolics of commerce, and are used primarily as modifiers of other phenolics in order to attain optimum flow-cure characteristics. Suitable catalysts for the reaction include the hydroxides of the alkaline-earth metals, and the alkali carbonates, among others. Ammonium hydroxide is generally unsatisfactory, probably because of the facility with which it condenses with furfural, and is thereby rendered ineffective. When an excess of furfural is employed in these alkaline-catalyzed reactions, the product is usually a mixture of very highly advanced resin and unchanged phenol. For this reason it has not, to date, been practicable to prepare satisfactory one-stage phenol-furfural resins comparable to the commercially available one-stage formaldehyde-phenolics.

From the standpoint of the resin manufacturer, furfural possesses certain advantages over formaldehyde. For example, shipping and storage economies are made possible by the fact that furfural is marketed in essentially anhydrous form. By the same token, kettle capacity is increased since no water of solution is introduced as in the case with formalin. Even the removal of water which is formed during reaction is simplified, inasmuch as it may be taken over, with furfural, in the form of an azeotrope which separates into two layers in the distillation receiver, the furfural layer being returned continuously to the reactor.[20, 21] Additionally, furfural has the important advantage over formaldehyde and other aldehydes of low molecular weight, of forming more resin per pound of phenol. Thus, at an aldehyde to phenol molar ratio of 0.85 to 1.0, 100 lbs. of phenol will produce 111–112 lbs. of resin when reacted with formaldehyde, and 171 lbs. of resin when reacted with furfural. This was of great importance during the war years when phenol was frequently in short supply, but beyond this, a simple raw material cost calculation reveals that phenol-formaldehyde resin is appreciably more expensive than related furfural types.

The earliest manufacturer of phenol-furfural resins was Durite Plastics, Inc. (see Novotny[22, 23, 24, 25, 26]), which concern produced molding com-

[19] Redman, Weith and Brock (to Bakelite Corp.), U. S. Pat. 1,924,514 (1933); *C. A.*, **27**, 5492 (1933).

[20] Kurath (to Economy Fuse and Mfg. Co.), U. S. Pat. 1,969,890 (1934); *C. A.*, **28**, 6330 (1934).

[21] Novotny (to John S. Stokes), U. S. Pat. 1,793,715 (1931); *C. A.*, **25**, 2312 (1931).

[22] Novotny, U. S. Pats. 1,398,147–149 (1922); *C. A.*, **16**, 802–3 (1922).

pounds possessing a flat viscosity curve at temperatures just above the fusion point, and a very steep viscosity curve at more elevated temperatures. In other words, the compounds exhibited unusually long flow characteristics at the lower molding temperatures, but could be converted to infusibility rapidly at temperatures (350–400°F.) somewhat higher than normally applied with phenol-formaldehyde resins. In molding technology, the relation between flow, viscosity and rapidity of setting is obviously very important, and is one of the major factors governing the usefulness of a resin. In many applications, the very short flow interval and rapid cure of phenol-formaldehyde resins is very desirable, but for certain others, as in deep-draw molding, a longer period of flow is required. Accordingly, the phenolic resin industry now makes use of combination formaldehyde and furfural phenolics in numerous instances, and in various ratios to produce molding compounds with a wide range of flow-cure characteristics. Other applications of the blends include binders for resinoid abrasive wheels, brake linings, adhesives and laminating varnishes.

The role of furfural in the development of long-flow, blended phenolic molding compounds is well recognized in the industry. Such blends helped make possible the first giant-size moldings, the deep-draw molding of large television console cabinets and other complex items which could not have been manufactured in this manner a mere five years ago. Approximately one-fifth to one-fourth of the total phenolic molding powder produced in 1950 contained phenol-furfural resin as a modifier, and an increase to about one-third is anticipated in the year 1952. The importance of long-flowing, fast-curing phenolics to the industry is increasing rapidly, and these figures are indicative of the value of furfural-phenolics as economical blending agents which impart optimum molding characteristics.

There is, however, a substantial market for phenol-furfural resins as other than modifiers of other phenolics—in applications where furfural is the primary or sole aldehyde component. For example, furfural-phenolics are being used as such for the production of molding powders for use in a number of operations. For the most part, it is presumed that these involve the molding of thick castings and parts with heavy sections. Admittedly, at normal molding temperatures this practice entails some sacrifice in rate of cure by comparison with formaldehyde-phenolic molding powders. On the other hand, the slower cure permits better heat penetration of the whole mass, and lessens the degree of "case-hardening" of the heavy molded article.

Unblended furfural-phenolics also appear to be particularly well-adapted

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[23] Novotny, U. S. Pat. 1,451,783 (1923); *C. A.*, **17**, 2035 (1923).

[24] Novotny and Romieux, U. S. Pat. 1,557,318 (1926); *C. A.*, **20**, 97 (1926).

[25] Novotny and Romieux, U. S. Pats. 1,597,538–9 (1926); *C. A.*, **20**, 3355 (1926).

[26] Novotny and Kendall (to John S. Stokes), U. S. Pat. 1,705,493 (1929); *C. A.*, **23**, 2310 (1929).

for use in molding compounds containing a high proportion of mineral filler. Compositions prepared in this manner show little or no tendency to stick to the mold during the curing cycle. One user has reported that they do not seem to "dry out" on the surface, but leave a resin film on the filler which permits clean release from the mold. Probably this practical observation can be explained in terms of better "wetting" of the mineral filler by furfural-phenol resin. The same characteristics have been noted with blended phenolics which contain an appreciable amount of furfural-phenol resin.

A fluid, phenol-furfural resin is widely used in the manufacture of asphaltic storage-battery cases.[27] Processing conditions require a resin which is compatible with asphalt, which will not "set" in the molding operation where a temperature of 300°F. is attained, but will cure rapidly at approximately room temperature when battery acid is introduced in the final assembly operation. The furfural resin is more applicable in these circumstances than formaldehyde-phenolics. In practice, it increases the resistance of the battery case to penetration by aqueous sulfuric acid, which otherwise attacks the organic fiber in the composition with resultant deterioration of the case.

Furfural has also found an important outlet in connection with the production of phenolic laminating varnishes. Compared to the more common cresol-formaldehyde compositions, varnishes prepared from furfural with lesser amounts of formaldehyde in combination with phenol have been found to possess equivalent electrical and superior mechanical properties. On account of these and other desirable properties, such varnishes have found industrial acceptance in connection with canvas and paper laminating operations despite their inherently darker color. Some of their properties have been discussed by Kline.[28]

The dark, viscous liquids, and fusible and infusible solid compositions obtainable from furfural and cashew nut shell oil exhibit interesting properties, difficult to achieve with other aldehydes and other phenolic compounds. Thermally stable resins of high and uniform frictional characteristics have been prepared which have become definitely established in the United States and Europe as versatile materials for the manufacture of friction elements in the automotive and aeronautical industries. The viscous, liquid resins are particularly adaptable for use in the production of brake linings by the die extrusion method, and by the sheeting or roll-milling technique. Thus, the lining ingredients are thoroughly mixed, extruded to size, and then shaped and cured. Alternatively, the mix may be sheeted to appropriate thickness, cut to the desired dimensions and then cured. If desired, the dry process of manufacture can be employed by using fusible-

[27] Dillehay (to Richardson Co.), U. S. Pat. 2,501,995 (1950); *C. A.*, **44**, 6056 (1950).
[28] Kline, *Modern Plastics*, **25**, No. 4, 101 (1947).

solid furfural-cashew nut shell oil resins. In these applications, the liquid or solid furfural resins may be used to replace all or part of the phenol-aldehyde resins previously employed. Infusible furfural-cashew nut shell oil resins are valuable, in pulverized form, as friction-modifying additives in the production of brake bands and clutch facings.[29]

Resins prepared by reacting phenol with bagasse are available which cure rapidly at relatively low temperature and pressure. The acidic conditions employed in the production of these products give rise to furfural by degradation of the pentosan constituents of the bagasse. Additional furfural is subsequently added in the presence of an alkaline catalyst, the amount being determined by whether thermoplastic or thermosetting compositions are desired. Dark colored, thermoplastic resins of this type are used as binders for phonograph records, and as plasticizers for shellac and vinyl compositions.

No attempt has been made to mention all of the industrial applications for furfural-phenolics, since their number is too great. It may be of interest to mention briefly, however, that during the war these resins were used for coating reaction vessels, food and beverage containers, paint and varnish cans, beer barrels and similar items. They have also formed the basis for combat helmit liners, ignition distributor heads, radio tube bases, shell and grenade fuses, tank periscope housings, washing machine agitators, and photodeveloping trays. Furfural resins have been employed as coatings to prevent water-seepage through stucco walls; they have been used for water-proofing textiles, and for impregnating wood for artificial ebony piano keys, cutting handles, and the like. Additionally, cold molded products of all kinds have been manufactured with furfural resins. A unique example is the cement used to attach incandescent light bulbs to the brass ferrule, an application which demands high resistance to moisture and heat, and excellent adhesion of the resin to both metal and glass, hot or cold.

Miscellaneous Furfural Resins

Acid-resinified Furfural

Furfural sets to an infusible and insoluble amorphous product when heated with any one of a variety of acidic catalysts (pp. 395–399). Attempts to make use of this property for the production of satisfactory castings have been unrewarding, but in recent years this type of furfural resin has found application in powder form as a friction-fortifying dust which is incorporated with the principal components (asbestos and resin binder) of friction elements, such as brake linings and clutch facings.[30] The purpose of these dusts, or friction modifiers, is to assist in maintaining a more or less uniform

[29] Harvey, M. T., private communication.
[30] Harvey (to Harvel Corp.), U. S. Pat. 2,383,790 (1945); *C. A.*, **39**, 5369 (1945).

frictional drag at various temperatures. The usefulness of the furfural resin lies in the fact that at temperatures in the neighborhood of 500–600°F., it softens slightly to a somewhat rubbery consistency. To obtain frictional characteristics at lower temperatures, additives such as vegetable oils, fatty acids, rubbers and pitches may be incorporated with the furfural prior to acid-resinification.

Yet another application for acid-resinified furfural is in manufacture of resin-impregnated carbon stock ("Karbate"[a]) for use in fabricating corrosion-resistant vessels, pipe, valves, heat exchangers, and other equipment for the chemical process industry. Ordinary carbon or graphite articles are porous, and permeable to a number of fluids, and furfural resin was the first synthetic resin to be employed to attain the desired degree of impermeability.[31, 32] Furfural containing a suitable catalyst is forced into the pores of the carbon stock, following which the impregnated article is subjected to elevated temperature and pressure to form and cure the resin *in situ*. The resulting Karbate is appreciably stronger than the original carbon stock, and finds application in process equipment for handling highly corrosive gases and liquids, including the absorption of hydrogen chloride in water. The relatively high resistance of acid-resinified furfural to chemical attack is, in large measure, responsible for its use in these applications. Also important are the effective wetting and penetrating properties of furfural prior to resinification.

Resins from Furfural and Alkyl Ketones

The condensation products of furfural with alkyl ketones (pp. 453–461) are sensitive to heat and acids, and the resulting resinous compositions have been the subject of considerable investigation, although no large scale uses have yet developed. Meunier[33] prepared varnish resins from furfural and acetone, as did Mains and Phillips[34] who also worked with furfural and methyl ethyl ketone. A patent was issued to Richardson[35] covering a molding composition comprising a furfural-acetone resin and suitable fillers. Resins derived from furfural and mesityl oxide are reported to possess film-drying properties.[36] Additional references which may be of interest include [37, 38, 39, 40].

[a] Trade name of National Carbon Company.

[31] Kiefer (to National Carbon Co.), U. S. Pat. 2,174,887 (1940); *C. A.*, **34**, 835 (1940).

[32] Hatfield and Ford, *Trans. Am. Inst. Chem. Engrs.*, **42**, 121 (1946).

[33] Meunier, *Mat. grasses*, **9**, 4516 (1916); *C. A.*, **10**, 1085 (1916).

[34] Mains and Phillips, *Chem. Met. Eng.*, **24**, 661 (1921).

[35] Richardson, U. S. Pat. 1,584,144 (1926); *C. A.*, **20**, 2082 (1926).

[36] Harvey (to Harvel Corp.), U. S. Pat. 2,461,510 (1949); *C. A.*, **43**, 3234 (1949).

[37] Turkington (to Bakelite Corp.), U. S. Pat. 1,677,417 (1928); *C. A.*, **22**, 3307 (1928).

[38] Beebe and Herlinger (to Wadsworth Watch Case Co.), U. S. Pat. 1,820,593 (1931); *C. A.*, **25**, 5741 (1931).

In recent years, interesting thermosetting resins have been prepared by reacting furfural (1 mole) with a suitable ketone (0.5 to 1.0 mole) in alkaline medium, and subsequently treating the product with formaldehyde (0.5 to 2.0 moles) in the presence of an acid catalyst.[41] These resins have been found to be compatible with synthetic rubber, and to impart to the rubber an increased resistance to attack by oils and miscellaneous chemical reagents.

When furfural-ketone resins, together with vinyl resins, are milled with acrylonitrile rubber (Hycar), very soft compositions are obtained, which are insoluble in petroleum solvents and useful in the manufacture of printing rolls.[42] Certain furfural-ketone resins are of value as frictional binders, their properties being dependent upon the structure of the ketone.[43]

The lacquer, "No-Wok",[b] which has been marketed for many years as a wear-resistant coating for lithographic plates, contains a resinous product derived from furfural and acetone.[38] The coating is light-sensitive, and following exposure to arc light becomes insoluble in gasoline, turpentine, and ink oils, so that the plates may be cleaned for re-use with little or no deterioration in quality.

Resins from Furfural and Nitrogen Compounds

The simplest isolable product from the reaction of furfural with ammonia is hydrofuramide (pp. 349–350). Though potentially available at comparatively low cost, and readily converted into resinous products, neither this compound nor its easily-formed isomer, furfurin, has found industrial acceptance to date, despite a great deal of effort on the part of numerous investigators (see, for example [13, 26, 44, 45, 46, 47, 48, 49]).

Neither is there any evidence at this time to indicate that the condensation product of furfural with amines (pp. 351–356) have been used industri-

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[b] Trade name of Wadsworth Watch Case Company.

[39] Moss (to Celanese Corp. of America), U. S. Pat. 1,902,256 (1933); *C. A.*, **27**, 3350 (1933).

[40] Goodhue (to the people of the U. S. for free use), U. S. Pat. 2,146,258 (1938); *C. A.*, **33**, 3517 (1939).

[41] Caplan and Harvey (to Harvel Research Corp.), U. S. Pat. 2,363,829 (1944); *C. A.*, **39**, 3697 (1945).

[42] Harvey (to Harvel Corp.), U. S. Pat. 2,545,461 (1951).

[43] Harvey (to Harvel Corp.), U. S. Pat. 2,461,508 (1949); *C. A.*, **43**, 3655 (1949).

[44] Cherry and Kurath (to Economy Fuse Mfg. Co.), U. S. Pat. 1,710,722 (1929); *C. A.*, **23**, 3060 (1929).

[45] Mains (to Westinghouse Elec. and Mfg. Co.), U. S. Pat. 1,835,510 (1932); *C. A.*, **26**, 1144 (1932).

[46] Bruins, *Iowa State Coll. J. Sci.*, **10**, 51 (1935).

[47] Berliner (to Canadian Industries, Ltd.), Canadian Pat. 321,629 (1932); *C. A.*, **26**, 3392 (1932).

[48] Taylor, U. S. Pat. 1,566,566 (1926); *C. A.*, **20**, 520 (1926).

[49] Beebe and Murray, U. S. Pat. 1,587,274 (1926); *C. A.*, **20**, 2292 (1926).

ally to any great extent as resin precursors, although a number of patents have been granted covering a wide variety of potential applications in the resin field (see, for example [50, 51, 39, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62]). Failure to find outlets is at least partly due to economic reasons, however, and not solely because of inherent defects in the resins themselves. This has certainly been true in connection with the potentialities of furfural-aniline resins in road construction and soil stabilization applications, although the subject is being reinvestigated at the present time in field studies concerned with the construction of both roads and airports.[63]

Most of us have seen roads constructed of gravel and some bituminous material go to pieces within a relatively short time. Many of such failures are due to poor bond between the gravel (mineral aggregate) and the bituminous binder, and this is particularly true with the so-called hydrophilic aggregates. Where available, hydrophobic aggregate of crushed stone is preferred because of its strong affinity for the bituminous coating. Winterkorn[64, 65, 66] (see also [67]) found that adhesion to hydrophilic-type aggregates is improved materially by treatment of the latter with furfural-aniline resins, or by immersion in furfural itself, and that such treatment is effective in preventing stripping of the bituminous coating under severe weathering conditions.

[50] Phillips and Mains, U. S. Pat. 1,441,598 (1923); *C. A.*, **17**, 1724 (1923).

[51] Moss and White (to Celanese Corp. of America), U. S. Pat. 1,902,255 (1933); *C. A.*, **27**, 3350 (1933).

[52] Ellis (to Ellis-Foster Co.), U. S. Pat. 2,037,710 (1936); *C. A.*, **30**, 4026 (1936).

[53] Dreyfus, U. S. Pat. 1,964,039 (1934); *C. A.*, **28**, 5238 (1934).

[54] Huxham, U. S. Pat. 1,606,943 (1927); *C. A.*, **21**, 333 (1927).

[55] Sutter (to Ciba Products Corp.), U. S. Pat. 2,034,597 (1936); *C. A.*, **30**, 3121 (1936).

[56] Cherry and Kurath (to Economy Fuse Mfg. Co.), U. S. Pat. 1,800,815 (1931); *C. A.*, **25**, 3503 (1931).

[57] Novotny and Vogelsang (to Durite Plastics, Inc.), U. S. Pat. 2,253,088 (1941); *C. A.*, **35**, 7978 (1941).

[58] Kienle and Scheiber (to General Elec. Co.), U. S. Pat. 1,812,749 (1931); *C. A.*, **25**, 5027 (1931).

[59] Kistler (to Norton Co.), U. S. Pats. 2,272,873–878 (1942); *C. A.*, **36**, 3649–3650 (1942).

[60] Sherrard, Beglinger, Hohf and Bateman (to Henry A. Wallace, Secretary of Agriculture of the U. S. A.), U. S. Pat. 2,137,119 (1939); *C. A.*, **33**, 1415 (1939).

[61] Beebe, Murray and Herlinger, U. S. Pat. 1,587,273 (1926); *C. A.*, **20**, 2292 (1926).

[62] Grimm and Rauch (to Rohm and Haas Co.), U. S. Pat. 2,205,355 (1940); *C. A.*, **34**, 7140 (1940).

[63] Mainfort, Civil Aeronautics Administration, Technical Development and Evaluation Center, U. S. Dept. Commerce, *Technical Development Report No. 136*, p. 14, Indianapolis, Indiana, February, 1951.

[64] Winterkorn, *Ind. Eng. Chem.*, **30**, 1362 (1938).

[65] Winterkorn (to The Quaker Oats Co.), U. S. Pat. 2,314,181 (1943); *C. A.*, **37**, 5215 (1943).

[66] Winterkorn (to The Quaker Oats Co.) Canadian Pat. 420,827 (1944).

[67] Janssen, *Roads and Streets*, **85**, 41 (September, 1942).

The process of incorporating some agent with natural soils which can then be compacted to form an integral material suitable for secondary roads or emergency air fields is known as soil stabilization. During the war this practice was studied by the U. S. Department of Commerce and included the testing of such agents as metal silicates, vegetable oils, and acid-catalyzed furfuryl alcohol resin. While promising results were reported in a number of instances,[68] none of these agents appeared to be as effective as a resin prepared from aniline (70 per cent by weight) and furfural (30 per cent by weight) by the action of aqueous aluminum chloride.[69]

While a variety of resins derived from furfural and urea, substituted ureas and thiourea have been described, apparently none of these has been commercialized to any extent, and it is considered pointless to discuss them here although the interested reader will find the following references pertinent:[70, 71, 72, 73, 74].

Furfuryl Alcohol Resins

Furfuryl alcohol has become more important than furfural in the resin field, the most important industrial developments involving the alcohol as the sole polymerizable source, although lesser applications have been made of combinations with formaldehyde, with urea-formaldehyde resins and others. Furfuryl alcohol resin, which is obtainable from several manufacturers[75, 76, 77, 78] is recognized as one of the lowest cost, heat-stable and corrosion-resistant polymers available at the present time. Accordingly, large scale uses have been developed, directly or indirectly connected with the fabrication of a wide variety of chemical processing equipment, including asbestos-filled cast-molded items, reinforced glass cloth, and resinous cements. Also of consequence are the applications wherein the resin is employed for the impregnation of porous substances, as a binder for porous glass fiber mats and low temperature curing adhesives, and as an additive

[68] Mainfort, Civil Aeronautics Administration, U. S. Dept. Commerce, *Technical Development Note No. 40*, pp. 8–12, October, 1945.

[69] Winterkorn, Civil Aeronautics Administration, U. S. Dept. Commerce, *Technical Development Note No. 43*, January, 1947.

[70] Novotny and Johnson (to John S. Stokes), U. S. Pat. 1,827,824 (1932); *C. A.*, **26,** 862 (1932).

[71] Novotny and Johnson (to John S. Stokes), U. S. Pat. 1,951,526 (1934); *C. A.*, **28,** 3606 (1934).

[72] D'Alelio (to General Elec. Co.), U. S. Pat. 2,300,208 (1943); *C. A.*, **37,** 1806 (1943).

[73] Mathis and Rampacek (to Phillips Petroleum Co.), U. S. Pat. 2,307,843 (1943); *C. A.*, **37,** 3918 (1943).

[74] Moss and White (to Celanese Corp. of America) U. S. Pat. 1,840,596 (1932); *C. A.*, **26,** 1812 (1932).

[75] Borden Company, Chemical Division, New York, N. Y.

[76] Durez Plastics and Chemicals, Inc., North Tonawanda, N. Y.

[77] Furane Plastics, Inc., Glendale, Calif.

[78] Irvington Varnish and Insulator Company, Irvington, N. J.

in asphaltic battery cases. There is good reason to believe that, over the past eleven years, the use of furfuryl alcohol resin in the construction of process equipment has helped materially to lower the tremendous costs inflicted annually on the chemical industry as a consequence of corrosion.

The resinification of furfuryl alcohol is readily accomplished in the presence of acidic catalysts. The chemistry of the reactions involved, and some of the numerous catalysts employed have been discussed elsewhere (pp. 220–224), but in practice, the resinification is generally stopped at an intermediate fluid stage by the addition of a suitable base to adjust the acidity. Within the range pH 5–8, the liquid resin is stable in storage for extended periods, and at the time of use, is recatalyzed with acid, following which it may be advanced through a rubbery stage to the final state of infusibility. The low molecular weight liquid resins are soluble in a variety of solvents including alcohol, acetone, the common esters, and benzene, the extent of the solubility varying inversely with the degree of resinification. The fully cured resins are dark-colored, thermally stable solids, notably inert toward solvents, acids and alkalies.

The rate of cure is largely dependent upon temperature and upon the activity and concentration of the acid catalyst. Strong mineral acids generally effect rapid cure. With milder acids (e.g., maleic, oxalic, and phosphoric acids) it is possible to prepare fluid resin systems which, at room temperature, show no appreciable change in viscosity over a period of several hours; with an acid as weak as acetic acid, it is practically impossible to reach a state of complete cure even at elevated temperatures. In this connection, it is interesting to note that some degree of stabilization of the liquid resin against further advancement by acids has been reported in instances involving the use of oxygenated solvents such as alcohols, ketones, and esters.

The necessity for relatively strong acid catalysts in order to effect complete cure has placed some limitations on the general applicability of furfuryl alcohol resins. That is, while fillers such as carbon, acid-washed asbestos, diatomaceous earth, and glass fiber can be used to extend or reinforce the resin, the deteriorating action of acid on cellulosic fillers (wood flour, canvas, paper, and the like) essentially prohibits the use of these materials. Additionally, it has been necessary to devise special molding and laminating techniques in several instances, in order to avoid corrosion of otherwise unprotected steel molds and platens. That such measures have been taken, however, testifies to the otherwise desirable characteristics of furfuryl alcohol resin.

Fluid furfuryl alcohol resins are compatible with a wide variety of plasticizers, thermoplastic and thermosetting synthetic and natural resins, synthetic rubbers, and asphalt, and in certain applications one or more of these materials has been added to improve toughness, flexibility, and ad-

hesion to non-porous surfaces. A number of chemically modified resins have also been prepared. For example, the resinification of furfuryl alcohol in the presence of formaldehyde[79, 80, 81] proceeds readily under somewhat milder acid conditions than are employed with the alcohol alone. As much as 0.6 mole of formaldehyde condenses per mole of furfuryl alcohol to give a resin which, in the completely cured form, exhibits essentially the same properties as furfuryl alcohol resin.[82] Urea can be added as a third ingredient to obtain a resin which is reported to be useful in fast-drying coating compositions.[83] Condensation of furfuryl alcohol with phenolic compounds also gives rise to interesting resins,[84, 85] but no known applications of these types exist today.

Resinous Cements

Corrosion-resistant resinous cements are prepared by mixing an inert filler, such as carbon or silica, with an acid catalyst and a fluid resin. Two major types are in general use, those in which the resin is a phenolic, and cements based on furfuryl alcohol resin. The former are resistant to acids (except oxidizing acids), and to mild non-caustic alkaline solutions, and are generally inert toward the common organic chemicals. They exhibit good heat resistance (360°F.), and possess low porosity and high strength characteristics. The properties of the furfuryl alcohol resin cements are very similar in all of these respects, but a marked superiority is noted with reference to alkali resistance. Thus, they are able to withstand the action of hot, concentrated, aqueous sodium or potassium hydroxide.

Furfuryl alcohol resin cements (see, for example [87, 88, 89]) began to be used extensively early in the 1940's, and descriptions of particular applications have appeared in several published articles.[90, 91, 92, 93, 94] The cements

[79] Zerweck, Schubert, Heinrich and Pinten (to General Aniline and Film Corp.), U. S. Pat. 2,306,924 (1943); *C. A.*, **37**, 3533 (1943).

[80] Harvey (to Harvel Research Corp.), U. S. Pat. 2,343,972 (1944); *C. A.*, **38**, 3391 (1944).

[81] Harvey (to Harvel Research Corp.), U. S. Pat. 2,343,973 (1944).

[82] The Quaker Oats Company, unpublished work.

[83] Root (to Ellis-Foster Co.), U. S. Pat. 2,335,701 (1943); *C. A.*, **38**, 3053 (1944).

[84] Korten (to General Aniline and Film Corp.), U. S. Pat. 2,321,493 (1943); *C. A.*, **37**, 6769 (1943).

[85] Delmonte (72% to Ralph Hemphill), U. S. Pat. 2,462,054 (1949); *C. A.*, **43**, 3655 (1949).

[86] The Atlas Mineral Products Company, "Atlas Corrosion Proof Cements," *Bulletin No. 5-1*, Mertztown, Pa., 1950.

[87] Kiefer (to National Carbon Co.), U. S. Pat. 2,174,886 (1940); *C. A.*, **34**, 835 (1940).

[88] Payne and Seymour (to The Atlas Mineral Products Co.), U. S. Pat. 2,366,049 (1943); *C. A.*, **40**, 503 (1946).

[89] Kauth (to General Cable Corp.), U. S. Pat. 2,323,333 (1944); *C. A.*, **38**, 271 (1944).

[90] Delmonte, "Modern Plastics Encyclopedia," p. 73, New York, Plastics Catalogue Corp. (1947).

[91] Runk, "Modern Plastics Encyclopedia," p. 85, New York, Plastics Catalogue Corp. (1947).

TABLE 1. PROPERTIES OF CARBON-FILLED FURFURYL ALCOHOL RESIN CEMENTS*

Tensile strength, psi	1500
Compressive strength, psi	12000
Flexural strength, psi	1500
Adhesion to wire-cut acid brick, psi	500–750
Coefficient of expansion, °F	$6–18 \times 10^{-6}$
Recommended service temperature (max.), °F	300–380
Density, lbs./cu. ft	90–95
Water absorption, % by weight	<0.5
Shrinkage on setting	nil
Working time† (minutes) at 60°F	90
Working time† (minutes) at 70°F	60
Working time† (minutes) at 80°F	30
Hardening time‡ (hours) at 60°F	48
Hardening time‡ (hours) at 70°F	20
Hardening time‡ (hours) at 80°F	12

* For the most part these data were taken from [86].
† Time that mortar remains in workable condition.
‡ Time required for cement to harden thoroughly.

are notably resistant to attack by a wide variety of chemical compounds, but for specific recommendations, it is advisable to consult with suppliers.[95, 97, 98, 77, 99, 100, 101, 102, 103, 104] While used largely to bond corrosion-resistant tiles or bricks, the cements are frequently employed to provide a secure backing for attaching the brick to the basic structure; in some instances the cement is used over a membrane of rubber or vinyl resin sheeting, a procedure especially recommended to minimize corrosion in tanks wherein a head of corrosive liquid may result in seepage through imperfections in the brick linings. Important applications include the construction of brick-lined reactors, storage tanks, absorption towers, fume stacks and the like, employed widely in the chemical industry, as well as the pickling tanks and trenches in use in steel mill operations. The very stringent sanitary regulations imposed on food and beverage manufacturers, and on meat packers, have been met with furfuryl alcohol resin cements in connection with the constructions of acid-proof tile floors. Brick or tile floors cemented in this manner are non-absorbent, and resistant to acids and alkalies, organic

[92] Meier, *Chem. Eng.*, **54**, 116 (December, 1947).
[93] Tucker and Werking, *Paper Ind. Paper World*, **28**, 60 (1946).
[94] Payne, *Ind. Eng. Chem.*, **40**, 1778 (1948).
[95] The Atlas Mineral Products Company, Mertztown, Pa.
[97] Ceilcote Company, Cleveland, Ohio.
[98] Electrochemical Supply and Engineering Company, Emmaus, Pa.
[99] Haveg Corporation, Newark, Del.
[100] Maurice A. Knight Company, Akron, Ohio.
[101] Nukem Products Corporation, Buffalo, N. Y.
[102] Pennsylvania Salt Manufacturing Company, Philadelphia, Pa.
[103] Stebbins Engineering and Manufacturing Company, Watertown, N. Y.
[104] U. S. Stoneware Company, Akron, Ohio.

solvents and live steam (see [105]), and some installations of this kind have been in continuous use for fifteen years or more. In the pulp and paper industry they have found widespread acceptance as cements for the brick linings in pulp storage tanks and towers, and in the huge digesters employed in the sulfite, sulfate, and magnesia pulping processes. This type of construction was used in one of the largest ceramic lining installations in the world (see [106]).

In conjunction with plasticized sulfur cement the furfuryl alcohol cements have been used for producing chemically resistant joints for vitrified clay pipe lines carrying industrial wastes. The annular space of the pipe is filled with sulfur cement after trowelling in a fillet and bead of the alcohol cement. The sulfur composition lowers the cost and advantage is taken of the heat of the molten sulfur cement in accelerating the cure of the furfuryl alcohol resin. Joints so prepared are quite rigid, and it is customary to lay the pipe on a concrete base to avoid breakage of joints due to settling.

Furfuryl alcohol resin cements have also been used directly as protective linings without brick or tile. For this purpose, the cement is generally reinforced with glass fabric in order to minimize brittleness and shrinkage, a practice which was probably first introduced in connection with the manufacture of armored stoneware piping. Additionally, a means has been devised, using expendable molds, for producing piping and ducts from fabric impregnated with resin cement. By this technique, it has been possible to fabricate, at low cost, comparatively large equipment which is molded in one piece with no seams or joints. One example is the construction, in this manner, of the Rauh-Klein muriatic acid absorber. Strong, and self-supporting, the cement-glass fabric material is used in the construction of pickling tanks, fume ducts, reels, and many other items required by the chemical, metallurgical and textile industries.

Cast Molding

Acid-catalyzed furfuryl alcohol resin filled with acid-washed asbestos is the basis for the cast-molded equipment known to the industry as "Haveg" 60. The molding process differs from conventional hot-molding practice in that light and inexpensive molds are used, and curing is carried out by heating at low pressure in large oven-type autoclaves. "Haveg" 60, in the form of pipe, ducts, valves, vats, hoods and tanks, is widely noted for its resistance to corrosion. It is a good heat insulator, and is generally unaffected by thermal shock or sustained temperatures as high as 265°F. Because of its uniform composition, surface damage to equipment molded from "Haveg" 60 does not affect its resistance to chemical attack. "Haveg"

[105] Payne, in "Directory of Materials for the Construction of Chemical Equipment," *Chem. Eng.*, **53**, No. 11, 116 (1946).

[106] Payne, *Ind. Eng. Chem.*, **41**, 2100 (1949).

41 is similar to "Haveg" 60, but involves the use of phenol-formaldehyde resin. Comparative physical properties of the two products are listed in Table 2. Neither is recommended for use with strong nitric or chromic acids, concentrated sulfuric acid, sodium hypochlorite, bromine, iodine, aniline or pyridine, nor may they be used with fluorine compounds which attack the asbestos. On the other hand, they are outstandingly resistant to a host of chemical compounds difficult to handle in other types of equipment. Each grade has its preferred applications, and specific information can be obtained from the manufacturer.[99]

TABLE 2. PHYSICAL PROPERTIES OF HAVEG[107]

	"Haveg" 60 (furfuryl alcohol resin)	"Haveg" 41 (phenolic resin)
Average density (lbs./cu. in.)	0.063	0.061
Strength characteristics (psi, at 70°F.)		
tensile	4,000	4,500
compressive	11,500	11,500
flexural	7,500	6,500
shearing	3,500	3,000
modulus of elasticity	1,580,000	1,880,000
Rockwell hardness ("R" scale)		
75°F	106	110
150°F	99	98
225°F	78	91
Thermal conductivity (B.t.u./sq. ft./hr./foot of path)	0.203	0.203

Impregnating Solutions

The ease of resinification of furfuryl alcohol, and its excellent wetting and penetrating properties have led to its use in formulating impregnating solutions. For example, by dissolving the alcohol in some suitable medium containing an appropriate concentration of acid catalyst, it is possible to obtain solutions of low viscosity which are relatively stable at room temperature. Such solutions may be employed to impregnate porous stoneware, for instance sandstone, following which the application of heat causes resinification to occur *in situ*. The resulting resin-impregnated product is non-porous, has considerably enhanced physical strength, and is vastly improved in its resistance to corrosion. Laboratory table tops and ceramic sinks have been produced in this general manner for many years.[108, 109]

[107] Haveg Corporation, "Corrosion Resistant Equipment," *Bulletin F-6*, Newark, Del., 1950.

Low-viscosity furfuryl alcohol resins are also good wettants and penetrants. Properly catalyzed, they may be used to make wood or concrete tanks impervious to liquids such as oils, acids and chlorinated hydrocarbons.[110] Considerable interest has also been shown in the use of these resins to strengthen plaster molds or objects. The impregnated plaster has excellent dimensional stability, is waterproof, and is resistant to chipping.[111] It is possible, in this manner, to produce artware objects which resemble ceramics in appearance.

Glass Fiber Pipe Wrap

Glass fiber mats bonded with furfuryl alcohol resin represent yet another material useful in many instances where corrosive liquids or vapors are encountered. The bonded mat is used to wrap around steel pipe which has been previously coated with bitumen or coal tar pitch. Such coated and wrapped pipe is intended for underground use, and is thus protected against chemical and electrolytic corrosion. The mats possess high tensile strength, and are wet rapidly and completely by the bitumen over a wide range of application temperatures so that the bitumen coating is strongly reinforced.

This application is representative of the use of furfuryl alcohol resin in emulsion form. Furfuryl alcohol is heated with aqueous acid in the presence of an emulsifying agent. The resin emulsion so obtained is applied to glass fiber matting and heated to remove water and cure the partial polymer.[112]

Battery Case Manufacture

A fluid furfuryl alcohol resin, adjusted to pH *ca.* 7.0 in order to minimize further polymerization even at temperatures as high as 300°F., has found application as an additive in the manufacture of asphaltic storage battery cases.[27] In recent years, this has been an important outlet for the resin, the purpose of which is to increase the resistance of the molded case (asphalt, resin, mineral filler and reinforcing organic fiber) to the action of battery acid, by inhibiting absorption of the acid by the organic fiber. While stable to advancement during the period of processing and molding, the neutralized, furfuryl alcohol liquid resin is immediately attacked on introduction of the battery acid, whereupon it seals off and protects the absorptive organic fibers.

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[108] Campbell (to Kewaunee Manufg. Co.), U. S. Pat. 2,333,151 (1944); *C. A.*, **38**, 1921 (1944).

[109] Reineck (to Kewaunee Manufg. Co.), U. S. Pat. 2,367,312 (1945); *C. A.*, **39**, 2765 (1945).

[110] Delmonte, *Plastics (Chicago)*, **1**, No. 5, 39 (1944).

[111] Delmonte, *Automotive and Aviation Ind.*, **93**, No. 11, 32 (1945).

[112] White and Smucker (to Owens-Corning Fiberglas Corp.), U. S. Pat. 2,397,453 (1946); *C. A.*, **40**, 3544 (1946).

Adhesives

In the aircraft industry, acid-catalyzed furfuryl alcohol liquid resin is the basis for a special low-temperature setting adhesive for bonding wood and plastic parts subject to warping or other deformation at elevated temperatures.[113] This adhesive, the so-called Resin X-2,[c] is a liquid, thermosetting resin (potentially 100 per cent solids) which is storage-stable, and and which at the time of use, is activated by incorporation of sufficient catalyst to permit curing at essentially room temperature (>75°F.). Since it contains little or no volatile products, the adhesive may also be employed for bonding rough or porous surfaces by the cast-gluing technique. As has been shown elsewhere,[114, 115] the glue line thickness is not critical with an adhesive which contains no volatiles.

Miscellaneous Uses

While no attempt at completeness has been made, it seems worthwhile to mention here a few of the lesser applications of furfuryl alcohol resins. Thus, they have been used to reinforce silica and Pyrex tubes and ceramic ware, to protect these items from physical shock.[116, 106] They may be incorporated into pitch, rubber and even oils to confer certain desirable properties, as for example, the application of the polymer as a pour depressant in waxy lubricating oils.[117]

For a number of years furfuryl alcohol has been applied to wooden table tops followed by application of mineral acid, and possibly another coating of the alcohol. In 1939, a laboratory supply house marketed furfuryl alcohol for refinishing laboratory table tops in this general manner.[118] Keminize finish[119] represents another application as a protective coating, which combines furfuryl alcohol resin with polymers of vinyl acetate and vinyl chloride. In general, furfuryl alcohol resins adhere strongly to wood and to concrete, whereas good bonding to metal and other non-porous surfaces has, to date, been difficult to achieve. Recent investigations, however, suggest that special primers may be effective in overcoming this difficulty.

[c] Trade name of Furane Plastics, Inc.

[113] Delmonte (to E. F. Lougee and Ralph Hemphill), U. S. Pat. 2,423,139 (1947); *C. A.*, **41**, 6076 (1947).

[114] Eickner, *Air Force Technical Report No. 5928*, U. S. Air Force, Air Material Command, Wright-Patterson Air Force Base, Dayton, Ohio, August, 1949.

[115] Simonds, Weith and Bigelow, "Handbook of Plastics," 2nd Ed., p. 694, New York, D. Van Nostrand Co. (1949).

[116] Uhlig, *Chem. Eng. News*, **27**, 2764 (1949).

[117] Lieber and Thorner (to Standard Oil Development Co.), U. S. Pat. 2,334,565 (1944); *C. A.*, **38**, 3831 (1944).

[118] Central Scientific Co., "Cenco News Chats," p. 22, Chicago, April, 1939.

[119] Lewis (to the Institute of Paper Chemistry), U. S. Pat. 2,267,830 (1942); *C. A.*, **36**, 2647 (1942).

APPENDIX

FURAN RESIN PATENTS

(Abstracts of the patents cited are available from The Quaker Oats Company, Chemicals Department)

Subject	*Patents*
Abrasive materials	
furan derivatives + anacardic acid	2,256,349
furan derivatives as plasticizers	2,449,058
furfural + an aminotriazine resin	2,215,380
furfural-aminotriazine resin	2,262,728; Can. 432,117
furfural and/or furfuryl alcohol resins	2,174,886–7; Can. 435,119
furfural or furfuryl alcohol as a plasticizer and solvents for	2,334,526; Can. 260,384
furfural and/or furfuryl alcohol + glycerine	Can. 435,119
furfural + aromatic amine + organic aliphatic chorinated polymer	2,414,748
furfural + aromatic amine	2,272,873–4–5–6–7–8; 2,309,575
furfural-cresol resin	2,314,349; 2,347,662
furfural + phenolic resin	Reissue 19,318; 1,537,454; 1,650,133; 1,893,117
furfural resins as a bond for	1,900,386; 1,901,324–5; 1,909,784; 2,111,248; 2,253,088; 2,272,873–4–5–6–7–8; 2,306,077; 2,314,349; 2,347,662; British 561,736; 563,123–4; 563,344
furfural as a wetting agent	Reissue 19,318; 2,200,164; 2,209,292
furfuryl alcohol-lignin resin	2,377,995
furfuryl alcohol as a wetting agent	1,924,748
furfuryl alcohol-furfural-lignin	2,421,623
furfuryl alcohol-resorcinol-aldehyde resin	2,470,440
phenol-aldehyde reins	2,448,985
phenol-furfural resins	2,175,480
Acetals	
polymerized with furfural	2,387,833
Acetate, vinyl	
polymerized with β-furylacrylic acid	2,346,858
Acetic acid, reaction with	
furfural	2,341,016; 2,408,615
furfuryl alcohol	2,433,645
Acetone	
as a solvent for furan resins	2,345,611
as a solvent with furfural for phenolic resins	1,785,641
Acetanilide, reaction with furfural	2,292,334
Acetone, reaction with furfural	1,482,929; 1,584,144; 1,587,269; 1,587,274; 1,677,417; 1,820,593; 1,902,256–7; 2,057,690; 2,146,258; 2,363,829; French 472,384; German 386,013
Acetonitrile, reaction with furfural	2,341,016
Acetophenone, reaction with furfural	2,146,258

Subject	*Patents*
Acetyl carbamid, reaction with furfural	1,827,824; 1,951,526
Acrylic acid	
allyl esters + vinylfuran	2,295,923
ethylidene esters + vinylfuran	2,284,639
Acrylic acid, reaction with	
furfuryl alcohol	2,332,461
Acrylic acid esters, reaction with	
furfuryl alcohol or tetrahydrofurfuryl alcohol	2,109,877
Adhesive mixtures	
amino-furfural	2,492,510
aminotriazine + furfural	2,388,143; Can. 432,117
formaldehyde + phenol + furfural	1,650,133; 2,397,627
furfural-acetone or furfural-aniline or furfural-phenol resin + vinyl compound + cellulose derivative	1,902,257
furfural-aromatic sulfonamide resin + cellulose derivative	1,840,596
furfural + casein + filler	1,813,377
furfural + a ketone	2,146,258
furfural + an aromatic amine	1,696,490; 2,146,257; British 563,124; 563,344
furfural-phenol resin with rubber	2,575,265; 2,397,627
furfural + phenolic material	2,186,369; 2,394,375; 2,397,627; 2,561,215; 2,499,134; 2,411,878; 2,443,197; 2,478,943
furfural + starch	2,141,313
furfural + urea + filler	2,413,624
furfuryl alcohol + urea-formaldehyde resin	2,518,388
Alcohol, ethyl	
as a solvent for furan resins	2,345,611
Alkyd resins	
furfural-phenol resin used with	2,314,349
Alkyl furans	
resins from	2,486,392
Alkylation	
of furfural resins	2,259,980; 2,599,347
Amide, reaction with	
acid salt of, + furfuryl alcohol or furfuryl alcohol and furfural	British 549,515
furfural	1,940,383; 2,205,355; 2,320,817; 2,322,566; 2,328,901; 2,331,376–7; 2,359,166; 2,377,867; 2,523,470
Amidine thiocyanates, reaction product with furfural	2,412,984
Amines	
acid salt of, + furfuryl alcohol or furfuryl alcohol and furfural	British 549,515
aliphatic, reaction with furfural	1,696,490; 2,205,355; 2,328,901; French 472,384

Subject	*Patents*
aliphatic, reaction with furylacrolein	2,058,771
aromatic, reaction with furfural	1,441,598; 1,515,642; 1,541,336; 1,587,269; 1,587,273–4; 1,594,982; 1,606,943; 1,678,085; 1,696,490; 1,800,815; 1,812,749;1,894,580; 1,895,945; 1,896,069; 1,902,255 1,982,486; 2,029,954; 2,037,710; 2,041,330; 2,137,119; 2,140,258; 2,146,257; 2,205,355; 2,228,567; 2,272,873–4–5–6–7–8; 2,275,293; 2,327,772; 2,328,901; 2,359,166; 2,389,150; 2,414,748; 2,429,554; 2,432,544; 2,530,107; British 563,124; 563,344; 587,303; French 683, 075
N-alkenylarylamine, reaction with furfural	2,495,890
aromatic, reaction with furfural + carboxylic acid	1,800,815
furfural + formaldehyde	2,013,589; 2,034,597; 2,041,330; 2,118,482
aromatic, containing one or more furyl or tetrahydrofuryl groups	2,364,350
cyclic reaction with furylacrolein	2,058,771
poly, reaction with hydroxy-furfural	2,181,121
Amines, reaction with	
furfural	1,737,391; 1,917,804; 2,205,355; 2,359,166
furfural + sulfamic acid	2,377,867
Amino-azine, reaction with	
furfural + water soluble salt of sulfuric acid	2,407,599
Aminotriazine, reaction with (see Melamine)	
furfural	2,197,357; 2,199,803; 2,209,292; 2,215,380; 2,218,474; 2,229,265; 2,259,980; 2,262,728; 2,285,750; 2,291,080; 2,294,873; 2,315,402 2,320,818; 2,320,820; 2,327,771; 2,351,602; 2,388,143; 2,492,510; 2,553,386; British 486,519; Can. 432,117
furfural + furfuryl alcohol	British 486,519
furfuryl alcohol	2,197,357
Aminotriazole, reaction with	
furfural	2,320,820; 2,332,302; 2,332,303
Ammonia, reaction with	
furfural	1,398,146; 1,503,392; 1,566,566; 1,587,269; 1,587,274; 1,594,982–3; 1,693,939; 1,737,916; 1,886,353; French 472,384; 664,869
furfural-phenol-aldehyde	1,398,146; 1,710,722; 1,726,650

Subject	Patents
Anacardic acids, reaction with	
furan derivatives	2,253,088; 2,256,349; 2,306,077
furfural	2,523,623; British 636,695
Aniline, reaction with	
furfural	1,441,598; 1,541,336; 1,587,269; 1,594,982; 1,594,983; 1,606,943; 1,696,490; 1,812,749; 1,902,255; 1,964,039; 2,009,987; 2,037,710; 2,137,119; 2,146,257; 2,156,160; 2,212,866; 2,221,945; 2,228,567; 2,272,742; 2,272,873-4-5-6-7-8; 2,275,923; French 683,075
furylacrolein	2,058,771
Apparatus, molding	1,993,942
Asphalt	
furfural used with	2,415,697
furfural resins used with	2,501,995
Base and cation exchange resins	
aminotriazine-furfural resin + guanidine	2,285,750
furfural + a furan	2,455,282
furfural + 2-cyano-3-potassiumsulfo-3-α-furylpropionamide	2,372,233
furfural + indene or coumarone	2,469,472
furfural + mineral acid halide	2,408,615; 2,420,419
furfural + sulfonated compound	2,468,471
furfural-urea resin	2,485,485
furfural + wallaba resin	2,549,745
furfural, aminotriazine, nitroparaffin and hydrogen	2,553,386
furfural + sludge acid	2,538,553
furfural + guanidine (aldehyde or ketone) resin	2,515,116; 2,522,668
furfural + polyalkylene polyamine + nitroalkane	2,518,956
furfural resin treated with a sulfonating or phosphonating agent	2,525,247; 2,541,909
phenol + a furan	2,541,909
furfural + furyl substituted aliphatic amine	2,525,480
furfural-melamine condensation products used in	2,521,664
furfural-phenol condensation products	2,531,863; 2,541,909
sulfonated furans	2,402,510-11-12-13-14; 2,455,282; 2,468,471
Benzaldehyde, reaction with	
furan	2,306,924
furfural	1,873,599
Benzene	
as a solvent with a phenol-furfural resin	2,399,735

Subject	*Patents*
Benzene (sulfonated) reaction with	
furfural	1,770,635
Benzidine, reaction with	
furfural	1,587,273; 1,982,486
Benzoic acid, reaction with	
furfuryl alcohol	2,253,192
Benzophenone, reaction with	
furfural	2,146,258
Benzoyl carbamide, reaction with	
furfural	1,827,824; 1,951,526
Benzyl alcohol, reaction with	
furfuryl alcohol	2,321,493
Bituminous compositions	
furfural used with	2,314,181
Boxes, battery	
furfural resins used in	2,501,995
Brake linings, see Friction elements	
Butadiene, reaction with	
bis(tetrahydrofurfuryl oxythiono) disulfide as a modifier	2,376,338
n-butyl β-(2-furyl)acrylate	2,231,623
copolymer of butadiene + phenol-aldehyde resin	2,411,878
benzyl β-(2-furyl)acrylate	2,231,623
β-chloroethyl β-(2-furyl)acrylate	2,231,623
furfuryl acrylate	2,395,017
furan	2,008,491
furfural	2,483,903
furylacrylic acid	2,234,204; 2,333,403
furylacrylic acid esters	2,321,623; 2,333,403; 2,234,204; 2,279,293
3-furylbutadiene	2,383,425
phenolic material-furfural resin	2,411,878
tetrahydrofurfuryl methacrylate	2,476,027
vinylfuran	2,256,148; 2,313,233; 2,326,095; 2,375,140; 2,376,015; 2,376,963; 2,380,473–4–5–6–7; 2,380,905; 2,383,055; 2,383,425; 2,384,889; 2,388,372; 2,416,461; 2,431,216; British 487,604
Camphor, reaction with	
furfural-urea resin	1,827,824; 1,951,526
furfural-xylenol-formaldehyde resins	1,793,715
Carbinol, vinylethynyl, reaction with	
furylacrylates	2,358,444
Carbohydrate + nitrogenous material	1,801,053
Carboxylic acids, reaction with	
furan aldehydes	2,341,016

Subject	Patents
Carboxylic acids, ammonium salt of, reaction with	
furfural	2,222,354
furylacrolein	2,222,354
tetrahydrofurfural	2,222,354
Cashew nut oil, reaction with	
[cashew nut oil (chlorinated)] + furfural	2,399,735
furfuryl alcohol soluble resin + furfural	2,366,049
Cashew nut shell liquid, reaction with	
furfural	1,725,797; 1,821,095; 2,306,077; 2,317,585–7; 2,327,785; 2,341,115; 2,551,282
furfural and aniline	2,523,623
furfural and furfurylamine	2,253,088
furfural and a phenol	1,821,095; 2,317,587; 2,341,115
furfural and styrene	2,338,231
Cellular resins	
furfural used in	2,446,429
Cellulose, furfural resinified in presence of	1,558,442
Cellulose, derivative, reaction with	
furan	2,129,731
furfural + phenolic resin	1,697,870
Cellulose ester, reaction with	
furfural-acetone-aniline-phenol resin	1,902,256
furfural-acetone or aniline or phenol and vinyl resin	1,902,257
furfural-aminotriazine and alkyd resins	2,218,474
furfural-aniline phenol resin	1,902,255
furfural-aromatic amine resin	1,902,255
furfural-aromatic sulfonamid resin	1,840,596
furfural-casein reaction product	1,648,179
furfural-ketone resin	1,587,269; 1,902,256
furfural or furfural derivatives	1,558,442; 2,059,441; 2,118,838; 2,129,731
furfural-phenol resins	1,697,870; 1,785,641; 1,941,708
furfural-phenol and toluene-sulfonamid resins	1,873,848
furfural residue	2,059,441; 2,118,838
furfuryl alcohol-abietic acid-maleic acid reaction product	2,197,047
furfuryl alcohol-furfural partial condensate	2,095,250
Cement	
furfural and/or furfuryl alcohol resins	2,174,886–7
furfural-phenol resin as a rubber bond	1,931,309
rubber, comprising furfural and latex	1,566,566
α-Chloroacrylonitrile, reaction with	
butadiene and/or vinyl furan	2,384,889
Cloth, tracing preparation of	
furfural-melamine resins used in	2,537,111

Subject	*Patents*
Coating compositions	
cashew nut oil + furfuryl alcohol soluble resin + furfural	2,366,049
cashew nut shell liquid + furfural	1,725,797; 1,821,095
2,5-bis(hydroxymethyl)furan and α-furylglycolic acid used in	2,370,572
furfural + acetone	1,820,593
furfural + aniline	2,037,710
furfural-melamine resins	2,537,111
furfural + phenol resins	2,302,557; 2,563,897; Can. 329,708
furfural-phenol resins + glass fibers	2,549,017
furfural-phenol + polyvinyl compound	2,403,077
furfural, rubber, latex and water	1,566,566
furfural resin and rubber	1,931,309
furfuryl alcohol-polyvinyl butyral resins	2,465,710
furfuryl alcohol	2,448,397
tetrahydrofurfuryl alcohol + vinyl compounds	1,780,652
Coatings, wire	
furan resins used in	2,323,333–4; 2,432,623
Coloring material	
furfural resins used as	1,627,939; German 422,172
furfural used to produce	1,524,995; Can. 295,242
furfuryl alcohol used to produce	1,732,124
Continuous polymerization of	
furfuryl alcohol	2,570,027
Cresol, reaction with	
furfural	1,377,519; 1,398,146; 1,693,112; 1,705,493; 1,705,495; 1,717,614; 1,736,047; 1,737,121; 1,771,033; 1,785,641; 1,857,357; 1,917,248; 2,009,987; 2,034,457; 2,314,349; 2,345,611; 2,349,181; Can. 298,814; French 669,865; Swiss 86,308
(arrested prior to completion)	2,034,457
furfuryl alcohol	2,321,493
Color, painting	
furan carboxylic acid used in	327,494 (A.P.C.)
Cooling medium, used in making furan resins	1,776,366; 1,901,324
α-Cyanoalcohol esters, reaction with	
furfural cyanohydrins	2,379,297
Detergents, furfural used in preparing	2,244,512
Diamines, reaction with furans	2,339,769
Diazine derivative, reaction with	
furfural	2,312,689; 2,312,693; 2,312,703–5; 2,321,364; 2,324,289–90; 2,324,368; 2,328,962–4; 2,337,547; 2,352,943; 2,379,691; 2,392,837; 2,407,599; British 570,569

Subject	Patents
Dicyandiamide	
furfural + reaction product of D and an amine	2,389,150
Difurfural acetone, reaction with	
drying oil	2,330,337
olefins	2,055,456
Dimethylolurea (see Urea)	
Dressing for tree wounds	1,675,641
Dyes	
azo, furan derivatives used in	British 570,561
furfural + sulfur	1,884,762
Emulsifying agents	
furfural used in	2,403,343
Enamel	
furfural + polyvinyl acetal resin	2,114,877
furfural + cellulose acetate	2,059,441; 2,118,838
furfural + furfuryl alcohol + polyamide	1,732,124; 2,323,334
furfuryl alcohol + alkyd resin	2,323,333
Ethylene diamine, reaction with	
furfural	2,129,615
furylacrolein	2,058,771
Ethylene, reaction with	
vinyl thiolester of furoic acid	2,377,753
Ethylene vinyl organic ester	
furfural, reaction with	2,396,209
Ethylfurfural, reaction with	
phenol	1,737,121
Ethylfurfuryl alcohol, reaction with	
resin acids and maleic acid	2,089,375; 2,197,046–7–8–9
Ethylidene acrylate, methacrylate	
furylethylene, reaction with	2,284,639
Fibrous materials, treatment with	
furfural + aniline	2,212,866
furfural + furfuryl alcohol	British 565,340
furfural + phenol	2,170,755
furfuryl alcohol	2,397,453
hydrofuramide	2,212,866
Fillers for furan resins	
digester residue	2,397,323
extracted cottonseed hulls	1,863,540
infusible phenol-furfural resin	1,705,493
walnut shell, wood flour	2,413,624
waste wood, peat, etc.	Russian 47,078
Film compositions	
furfural used in	2,336,792; 2,411,878; French 678,688
Filtering material	
furfural, furfuryl alcohol and mineral wool	British 565, 340
furfural as a solvent for the binder	1,576,440
furfuryl alcohol + water + acid catalyst + mineral wool	2,397,453

Subject	*Patents*
Formaldehyde, reaction with	
furan	2,306,924
furfural + polyvinyl alcohol	2,464,717
furfuryl alcohol	2,429,329; 2,306,924; 2,343,973; 2,335,701; 2,383,792; 2,404,840
phenol + furfural	2,397,627
Friction elements	
furfural-phenol resins	1,672,538; 1,788,319; 1,950,262; 2,008,723; 2,175,480; 2,245,203
furfural used with phenol resins	2,185,333; 2,327,785
polymerized furans	2,383,790
Fur, treated with	
furfuryl alcohol	2,240,388
furfuryl alcohol ester	2,253,192
Furan aldehydes, halogenated as curing agents	2,561,814
Furans as resin catalysts	1,950,468; 1,975,246
Furans, reaction with	
acetone, benzaldehyde, or formaldehyde	2,306,924; 2,521,614
allyl ester derivatives	2,332,900
aryl diamines	2,536,107
guanamine derivatives	2,302,162
rosin	2,477,655
styrene	2,479,306
vinyl ester derivatives	2,326,048; 2,332,895-6-7-8-9-901
Furan	
resins from	1,665,233-4-5-6-7; 2,486,392
stabilization of	2,436,764
halogenation of	2,475,801; 2,490,462
Furans used as hardening agents	1,886,353; 2,490,462
Furan used as solvent for polymers	2,545,317; 2,554,973
Furan esters and miscellaneous furans	
allyl furoate	2,195,382; 2,308,495; 2,290,164
3-arylaminotetrahydrofuran	2,278,202; German 704,300
β-2-(5-chlorofuryl)acrylic acid	2,454,294
butyl furoate	2,129,731
chloroallyl furoate	2,205,390; 2,213,201; 2,311,607; 2,311,615; 2,321,896; 2,331,263; 2,341,175
cinnamyl furoate	2,195,382
citronellyl furoate	2,195,382
crotyl furoate	2,195,382
cyclopropyl furylpropenone	2,470,349
cyanohydrin of furfural	2,379,297
diamino-2-furo-triazine-1,3,5	2,302,162
difuroate of 1,4-dioxanediol-2,3	2,164,357; 2,186,359
difurfuralacetone	2,512,672
di-α-furyl ketone disulphonate	2,373,152
1,5-di-α-furyl-3-ketopentanedisulphonate-1,5	2,373,152
difurfurylidene pentaerythritol	2,223,421

Subject	Patents
Furan esters and miscellaneous furans (*cont.*)	
difuryl sulfonates	2,373,152; British 592,747
2,5-dimethoxytetrahydrofuran	2,585,596
ditetrahydrofurylethyl carbinol	2,455,392
ethyl furoate	2,129,731
fumaric monoacid N-furfuryl monamide	2,260,006; 2,377,866
furanacrylic acid	2,431,216
furancarboxylic acid	327,494 (A.P.C.)
furfuralacetone	2,512,672
furfural, substituted	2,363,615
furfurglycerol	2,512,672
furfuryl acrolein	2,264,034
furfuryl acrylate	2,109,877; 2,433,866
β-furfuryl acrylic acid	2,346,858
furfuryl α-chloroacrylate	2,247,790
furfuryl crotonate	2,260,005
furfuryl dicyandiamide	2,517,824
furfuryl-α,β-dichloroacrylate	2,337,681
furfuryl guanidines	2,517,824; 2,541,005
furfuryl methacrylate	2,057,673–4; 2,129,667; 2,296,403
furfural monoaryl hydrazone	2,537,648
furfuryl peroxycarbonate	2,370,588
furfuryl phthalate	2,253,192
furfuryl silicates	2,300,812
furfuryl trichloroacrylate	2,337,681
furfuryl urea, mono-	2,427,503–4
furfurylideneacetone	2,469,788; Dutch 62,117
furonitrile	2,302,162
furylacrolein	2,058,771; 2,222,354; 2,353,591
α-furylacrylic acid	2,454,294
β-furylacrylic acid	1,911,722; 2,333,403; 2,234,204; 2,364,358; 2,381,884; 2,382,297; 2,397,372; 2,425,756; British 569,525
β-furylacrylic acid esters	2,231,623; 2,234,204; 2,278,528; 2,279,293; 2,333,403; 2,358,444; 2,381,881; 2,454,756
β-furylacrylic glyceride	2,381,881; 2,382,297
β-furyl-α-alkylacrylic acid	2,364,358
β-furyl-α-phenylacrylic acid ethyl ester	2,276,176
furylethylene derivatives	2,527,714
furylbutadienes-1,3	2,194,416; 2,383,425; 2,384,239
1,5-di-α-furyl-3-ketopentane disulfonate-1,5	2,373,152
2,6-bis(α-furyl metal sulphomethyl) cyclohexanone	2,373,152
N,N′-bis-(furyloxymethyl)urea	2,374,647
2-furfuryl-(2)-dioxolane-1,3	2,526,601
pentaerythritol difurfural (acetal)	2,526,601
furfuryl guanides & biguanides	2,522,668

Subject	*Patents*
α-furylaldehyde sulphonates	2,402,510
α-furylamide sulphonates	2,402,512
α-furylcarboxylic acid sulphonates	2,402,511
α-furylglycolic acid	2,370,572; 2,384,119; 2,387,933
2-furylhexadiene-2,4-oic acid	2,381,880
2-furyl-1,3-ditolylimidazolidine	2,525,898
furyl isopropenyl ketone	2,278,638; 2,309,727
α-furyl fatty acid nitrile sulphonates	2,402,513
α-furylnitroethane sulphonates	2,402,514
furyl-oxy and furfuryl-oxy substituted acrylonitriles	2,385,258
5-(2-furyl)pentadien-2,4-oic acid	2,381,880
furyl sulfonates	2,373,152; British 592,747
furfuryl sulfenamides	2,581,905
2-furylvinyl isocyanate	2,326,287
furyl vinyl ketone	2,278,638; 2,309,727
geranyl furoate	2,195,382
2-hydroxyfurfural	2,181,121
2,5-bis(hydroxymethyl)furan	2,370,572; 2,384,119; 2,384,124; 2,387,933
1-hydroxymethyl-4-α-furylbutadiene	2,346,612
hydroxybenzofuran	2,260,006
itaconic monoacid N-furfurylmonoamide	2,260,006
methallyl furoate	2,195,382
methallyl furylacrylate	2,279,293
methyl furylacrylate	2,420,194
methyl β-(2-furyl)acrylate	2,231,623; 2,234,204
methyl phenoxyethyl furoate	2,331,263
polyvinyl furfural-acetaldehyde acetal	2,159,263; 2,146,735; 2,186,598
tetrahydrofuran	2,402,137
tetrahydrofurfuryl α-acetoxypropionate	2,222,363
tetrahydrofurfuryl acrylate	2,109,877; 2,229,997
tetrahydrofurfuryl chloroformate	2,370,588
tetrahydrofurfuryl ethenyloxyacetate	2,399,626
tetrahydrofurfuryl methacrylate	2,057,673–4; 2,129,666; 2,296,403; 2,476,027
thiofuran	2,533,764
bis(tetrahydrofurfuryl oxythiono) disulfide	2,376,338
trifurfuryl borate	2,276,094
unsaturated furoates	2,195,382
unsaturated resin acids	2,089,375; 2,197,046–7–8–9
vinylfuran	1,911,722; 2,256,148; 2,259,512; 2,278,528; 2,278,635; 2,284,639; 2,295,923; 2,313,233; 2,326,095; 2,375,140; 2,376,015; 2,376,963; 2,380,473–4; 2,380,475–6–7; 2,380,905; 2,383,055; 2,383,425; 2,384,889; 2,388,372; 2,390,446; 2,397,287; 2,401,769; 2,404,267–8; 2,404,292; 2,416,461; 2,419,057;

Subject	*Patents*
Furan esters and miscellaneous furans (*cont.*)	
vinylfuran (*cont.*)	2,419,347; 2,431,216; 2,442,283; 2,478,860; 2,483,182; 2,496,097; 2,546,220; German 677,868
1,5-pentanediol difuroate	2,504,930
o,o'-di(furamido)diphenyldisulfide	2,530,355
Furan resins used in plating baths	2,526,999
Furan resins, chlorination of	2,423,139
Furfuralacetone, reaction with	
amine, secondary	1,906,935
drying oil	2,330,337
Furfural, reaction with miscellaneous compounds (See also, index, under specific compounds)	
accroide gum	1,909,784; 2,300,307
acid solvent, in furfuryl alcohol reaction	2,416,038
acetone oil	French 472,384
acetals	2,146,735; 2,159,263; 2,186,598; 2,326,048
acetaldehyde	1,571,447; 1,592,296; 1,592,773; 1,873,599; German 539,475
acetanilide	2,292,334
acetic acid or anhydride	2,341,016
acetoacetanilide	2,292,334
(acetoacetyl), di-, ethylene diamine	2,292,333
acetonitrile	2,341,016
acetonylacetone	2,516,317
acetophenone	2,146,258
acetylides	1,963,934
acrylic esters	2,109,877
aldehydes	1,771,508; 1,793,715; 1,835,510; 1,857,357; 1,873,599; 2,194,416; 2,264,034; French 472,384; German 539,475
aldoketene	2,361,036
alkaline polysulfide	1,964,725; 2,363,616
n-alkenylarylamines	2,495,890
alkyl ester	2,332,900
alkyl halides	2,342,456; 2,357,635
alkyl sulfides	2,344,289
amide	1,940,383; 2,359,166
amidine thiocyanates	2,412,984
amido compounds	2,322,566
amidogen compound	2,320,817; 2,325,376
ammeline	2,456,567
anacardic materials	2,306,077
aryl compounds	2,322,567; 2,327,772
benzaldehyde	1,873,599
benzidine	1,587,273; 1,982,486
benzophenone	2,146,258

Subject	*Patents*
s-benzyl thioammeline	2,345,456
biguanide sulfanilamide	2,331,376; 2,331,377
boric oxide	2,241,676
brucite	2,241,676
butyl urethane	2,300,307
butylaldehyde	1,477,870
butylenes	2,227,311
butyl methacrylate	2,366,049
carbamides (see Urea)	2,407,599; 2,442,747; 2,471,188; German 507,419
carbazide derivative	2,328,957–962
cardanol, hydrogenated	2,284,369
carbohydrate	1,949,831
carbonyl compounds	2,544,308
carboxylic acids	2,207,626; 2,331,805; 2,341,016
cardanol	2,317,585
casein	1,648,179; 1,678,713; 1,711,025; 1,813,377
caseinate	1,752,580
cellulose acetate	2,059,441; 2,118,838
coffee bean ingredients	2,277,252; 2,340,426
coumarone—indene resins	2,104,829; 2,469,472
cresylic acid	2,089,813; 2,430,736; 2,467,498
crotonaldehyde	1,873,599
crotonic acid	2,341,016
cyanoacetamide	2,239,441
cyclic hydrocarbons	2,382,184
cyclohexanone	1,587,273
cyclopentadiene resins	2,104,829
cyamidine	1,441,598
diamines	2,292,333; 2,339,769; 2,340,045; 2,536,107
4,6-diamino pyrimidyl-2-cyanomethyl sulfide	British 561,992
4,6-diamino pyrimidyl-2-*p*-sulphamyl phenyl carbamyl methyl sulphide	British 570,520
diaminotetrazine	2,369,371
diazinyl derivatives	2,324,368; 2,328,962; 2,344,289; 2,393,753
diazinyl hydrazine derivatives	2,339,061
dicarbamido derivatives	2,340,045
dicarboxylic acid anhydrides	2,371,990
dicyandiamide	2,427,512
dicyandiamide + aromatic amine	2,389,150
diphenyl (hydroxy)	2,017,877
diphenylamine	1,982,486
diphenylolpropane	1,941,708
diphenylmethane, *p*-diamino	2,029,954
dumortierite	2,241,676
esters, organic	2,211,419; 2,325,376

Subject	*Patents*
Furfural, reaction with miscellaneous compounds (*cont.*)	
ethyl acetate	2,211,419
ethyl propionate	2,211,419
ethylenediamines	2,129,615; 2,292,333
ethylene-carbon monoxide polymers	2,351,120
furylamines	2,525,480
furfuryl alcohol	1,665,236–7; 2,095,250; 2,174,886; 2,267,830; 2,323,334; 2,333,151; 2,345,966; 2,366,049; 2,367,312; 2,416,038; 2,421,623; 2,423,139; 2,471,438; 2,471,600; 2,471,631; 2,499,275; 2,571,994; British 565,340; British 575,693; British 595,208; Can. 387,514; Can. 435,119
furylethylene derivatives	2,527,714
gluten	1,988,475
guanazo diazine	2,312,320
guanazole	2,378,199; 2,389,896
guanazo triazine	2,312,321
guanidine derivatives	1,496,792; 2,515,116
halogenated compounds	2,339,059; 2,340,107; 2,374,963
hydrogen sulfide	1,991,765; 2,019,354
hydroxydiphenyl	2,017,877
indene	2,469,472
kaolin	2,241,676
ketones	1,441,598; 1,482,929; 1,584,144; 1,902,256–7; 2,146,258; 2,191,802; 2,264,034; 2,363,829; 2,442,989; 2,515,116; French 683,075; German 386,013
ketone + aromatic amine	1,906,935; 2,327,771
lactide	2,174,491
lactic acid	2,207,626
latex	1,566,566
lignin sulphonic acid or salt	2,266,265
magnesium salts	2,241,676
malonic compounds	2,300,208; 2,239,441
melamine-formaldehyde condensate	2,562,051
mercaptoarylthiazole derivative	1,917,804
mesityl oxide	2,565,685
metals, reducing	German 307,662
methyl ethyl ketone	1,441,598
methyl acetate	2,341,016
methylene cyanide	2,239,441; 2,300,208
methylene diphenol	1,941,708
mono-amine derivative	2,339,770; 2,340,046
naphthalene (sulfonated)	1,770,635
naphthenic acids	2,207,624; 2,207,626
α or β-naphthylamine	1,441,598; 1,515,642; 1,587,273

Subject	*Patents*
nitriles	2,320,816
nitroalkane	2,518,956
nitroaniline	1,441,598
nitromethane	2,355,402
nitroparaffin	2,355,402; 2,553,386
nitropropane	2,355,402
olefins, aliphatic	2,055,456; 2,274,749
olefins, tertiary	2,386,055
paraconic acid, 2-oxo-4,5-diimino	2,514,353
paraldehyde	1,873,599
petroleum products	1,933,715–6; 1,952,060; 2,008,103; 2,035,123; 2,055,456; 2,146,276; 2,207,624; 2,227,311
phenol-cellulose combinations	1,721,315
phenol-monohydric and polyhydric	2,478,943
phenolic condensation products	2,462,636
phenylenediamine	1,587,273; 2,272,873
phosphorus amide	1,940,383
phosphorus oxychloride	2,408,615; 2,420,419
piperidine	1,678,085; 1,737,391
pitch, wood	2,141,043; German 352,521
polyalkyline polyamine	2,518,956
polyamide + amino compound	2,389,415
polyamine + hydroxyaromatic compound	2,459,112
polycarboxylic acids	2,395,739
polyricinoleic acid	2,403,343
polyvinyl alcohol	2,387,833; 2,399,401; 2,464,717
polyvinyl aryl compounds	2,363,297
polyvinyl esters	2,227,975; 2,269,216–7; 2,326,048; 2,366,049
polycyanoacetamido compound	2,471,243
prolamine	2,375,978
prolamine + a carbamide	2,427,503–4
pyridinium compounds	2,192,085
pyramidine derivatives	2,317,737; 2,340,107
pyrimidyl cyanoalkyl sulfides	2,317,736
pyrogallol	2,275,923
ricinoleic acid	2,403,343
rosin	1,894,580; 2,129,731; 2,229,265; 2,572,071; German 352,521
rosin acids	2,331,805
rubber	1,555,131; 2,522,349; French 584,678
saccharides	1,949,831; 1,974,064
sludge, refinery	2,538,553
starch	2,141,313
styrene	2,338,231
sulfamic acid	2,350,165
sulfamides, aryl	2,072,971; 2,365,599
sulfide, poly	1,964,725; 1,996,487; 2,363,616; 2,374,963

Subject	Patents
Furfural, reaction with miscellaneous compounds (*cont.*)	
sulfides	British 570,520
sulfonamide salts	2,331,377
sulfonamide, aromatic	1,840,596–7; 1,873,848; 2,327,772; 2,331,376; 2,545,174; Can. 303,697; German 569,021
sulfonamides	2,545,683; 2,545,716
sulfonated aromatic hydrocarbons	1,770,635; 2,468,471
sulfonates, furyl substituted	2,455,282
sulfone resins	2,146,276
sulfur	1,884,762
sulfurous acid salts	2,407,599
sulfuryl chloride	2,408,615; 2,420,419
talc	2,241,676
tannic acid	2,275,923
tannin	2,275,923
tar	German 352,521
tartaric acid	2,207,626
thiocyanate, aromatic amine	2,563,838
toluidine	1,441,598; 1,515,642; 1,587,273; 1,594,982–3; 1,606,943; 1,895,945
toluylenediamine	1,441,598; 1,587,273
triamine derivatives	2,339,768; 2,340,044
triazinyl cyanoalkyl sulfides	2,317,739
triazinyl derivative	2,320,819; 2,324,284
trioxymethylene	2,269,217
urethane	2,300,307; 2,321,761
vegetable material + chlorine	2,137,119
vinyl acetal resin	2,114,877
vinyl acetate	2,267,830; 2,332,895
vinyl acetylide	1,963,934
vinyl alcohol	2,044,730; 2,224,663; 2,332,895–6–7–8–9–900; 2,332,901; 2,378,535; 2,387,833
vinyl ester materials	Reissue 20,430; 2,036,092; 2,332,895–6–7–8–9–900–01
wallaba resin	2,549,745; 2,569,301
xylenol	1,679,312; 1,771,138; 1,771,508; 1,773,598; 1,793,715; 1,835,510; 1,980,987; 2,363,297; 2,378,199
xylidine	1,441,598; 1,587,273; 1,678,713; 1,902,255
Furfural used in	
electroplating baths	2,458,504
hardening agent	1,591,999; 1,886,353; 2,038,142; 2,127,894
preparing flame-resistant resins	2,396,575
purifying organic compounds	2,544,308; 2,554,089
oil purification system	2,425,085

Subject	*Patents*
resin solvent	1,576,440; 1,899,526; 1,963,579; 2,008,103; 2,366,049; 2,380,340; French 664,869; German 536,677
separation of tertiary olefins	2,386,055
Furfural-extracts from petroleums	
reaction with asphalt	2,415,697
Furfural-phenol resins	
demulsifiers, used in	Reissue 23,432; 2,499,360-1-2-3-4-5-6-7-8; 2,499,370; 2,524,889; 2,524,890-1-2; 2,541,990-1-2-3-4-5-6-7-8-9; 2,542,000-1-2-3-4-5-6-7-8-9; 2,542,010-11-12-13; 2,557,081; 2,560,333; 2,564,191-2-3; 2,568,115; 2,571,116-7-8-9; 2,571,120-1; 2,573,893; 2,574,536-8; 2,574,546-7; 2,574,817; 2,581,367-8; 2,581,370-1-2-3-4-5-6-7-8-9; 2,581,380-1-2-3-4-5-6-7-8-9; 2,581,390-2
oxyalkylation of	Reissue 23,432; 2,499,360-1-2-3-4-5-6-7-8; 2,499,370; 2,524,889; 2,524,890-1-2; 2,541,990-1-2-3-4-5-6-7-8-9; 2,542,000-1-2-3-4-5-6-7-8-9; 2,542,010-11-12-13; 2,557,081; 2,560,333; 2,564,191-2-3; 2,568,115; 2,571,116-7-8-9; 2,571,120-1; 2,573,893; 2,574,536-8; 2,574,546-7; 2,574,817; 2,581,367-8; 2,581,370-1-2-3-4-5-6-7-8-9; 2,581,380-1-2-3-4-5-6-7-8-9; 2,581,390-2
Furfural resins as a modifying agent	2,315,400; 2,320,816
Furfuramide	
use in a phenol-aldehyde resin	1,398,146; 1,705,493-5-6; 1,710,722; 1,726,671; 1,726,650; 1,737,916; 1,771,138; 1,773,598; 1,793,715; 1,835,510; 1,849,109; 1,950,262; Can. 280,359; Can. 280,543; Can. 280,746-7
Furfuramide, reaction with	
aldehyde	1,873,599
iodoform	1,587,274
phenols	1,398,146; 1,737,121; Russian 52,326
ureas	German 507,419

Subject	Patents
Furfurin, reaction with a phenol and aldehyde	Can. 321,629
Furfuryl alcohol, controlled resinification of	2,399,055; 2,416,038; 2,432,890; 2,445,137; 2,470,394; 2,471,438; 2,471,600; 2,553,677; 2,570,027; British 587,350; British 595,208; Can. 444,430
Furfuryl alcohol, resins from	1,665,235–6; 2,274,864; 2,234,565; 2,553,677; 2,570,027
Furfuryl alcohol, reaction with miscellaneous compounds (See also index under specific compound)	
acrylic acid	2,332,461
acyl isothiocyanate	2,327,985
aldehyde-ammonium thiocyanate resin	2,526,643
alkyd resins	2,323,333
ammonium thiocyanate	2,368,426; 2,526,644 British 634,126
amylaceous material	2,374,676
benzoic acid	2,253,192
benzyl alcohol	2,321,493
boric oxide	2,241,676
brucite	2,241,676
butyl methacrylate	2,366,049
carbohydrate derivatives	1,982,822
carboxylic compounds	2,437,955
crotonic acid	2,332,461
diaminotetrazine	2,369,371
diethyl carbonate	2,410,305
dumortierite	2,241,676
ethylenesulphonyl derivatives	2,348,705
filamentous materials	2,240,388
furfural	1,665,236–7;2,095,250; 2,174,886–7 2,267,830; 2,323,334; 2,333,151; 2,345,966; 2,366,049; 2,367,312; 2,416,038; 2,421,623; 2,423,139; 2,471,438; 2,471,600; 2,471,631; 2,499,275; 2,571,994; British 565,340; British 575,693; British 595,208; Can. 387,514; Can. 435,119
glyoxal	2,383,793
kaolin	2,241,676
lignin	2,538,302
lignin + amino triazine + aldehyde (furfural)	2,562,898
lignin-sulphonic acid or salt thereof	2,243,481
magnesium silicate	2,241,676
methacrylic acid	2,332,461
methyl methacrylate	2,129,667
phenol-formaldehyde resin	British 631,109

Subject	*Patents*
phosphonitrilic halide	2,214,769
phthalic acid and anhydride	2,253,192
polyvinyl acetal	2,432,623
polyvinyl butyral	2,465,710
polyvinyl esters	2,366,049
proteins	2,383,792; 2,420,736
resin acids	2,089,375; 2,197,046–7–8–9
resorcinol	2,321,493; 2,462,054; 2,470,440
salicylic acid	2,253,192
starch	2,374,676
succinic acid	2,253,192
sulfur dioxide	2,253,775
sulfur dioxide + light	2,192,467
talc	2,241,676
tetraethyl silicate	2,276,094
tributyl borate	2,276,094
unsaturated acids	2,332,461
urea-aldehyde resins	2,468,056; 2,487,394
urea-formaldehyde condensation product	2,468,056; 2,518,388
zein	2,185,216
Furfuryl alcohol-furfural resin-controlled resinification	2,471,600
Furfuryl alcohol as a resin solvent	2,348,705; 2,366,049; 2,565,602
Furfuryl alcohol, partially resinified, reaction with	
alkyd resins	2,323,333
ammonium thiocyanate	2,570,028
film forming substances	2,397,453
formaldehyde	2,343,972–3
formaldehyde + lignin	2,343,973
glyoxal	2,383,793
lignin	2,494,545
polyamide resins	2,323,334
polyvinyl acetal	2,432,623
polyvinyl butyral	2,465,710; British 593,477
phenolic substance	2,456,628
Furfuryl alcohol resin as a pour depressor for lubricating oils	2,274,864; 2,334,565
Furfurylamine, reaction with	
acyl isothiocyanate	2,327,985
anacardic acid	2,253,088
alkaline polyhalide	2,414,018
cashew nut shell liquid	2,253,088
phosphonitrilic halide	2,214,769
Furfuryl chloride, reaction with	
maleic acid	2,089,375; 2,197,046–7–8–9
resin acids	2,089,375; 2,197,046–7–8–9
Furoic acid	2,318,959; German 342,365; 386,013

Subject	Patents
Furoic acid, reaction with	
allyl alcohol	2,195,382
2,3-dichlorodioxane-1,4	2,614,357
geraniol	2,195,382
vinyl compounds	2,378,535
Furylethylene (see Vinylfuran)	
Furyl isopropenyl ketone	
polymerization of	2,278,638
reaction with an acrylic ester	2,309,727
Furyl vinyl isocyanate	
reaction with vinyl compounds	2,326,287
Furyl vinyl ketone	
polymerization of	2,278,638
reaction with an acrylic ester	2,309,727
Glass, artificial	
furfuryl alcohol used in making	2,332,461
furoic acid used in	2,318,959
vinylfuran used in	2,259,512
Glass fibers	
furfural-phenol resins used with	2,549,017
Glass, shatterproof	
furfural resins used in	1,840,596; 1,902,257; 2,159,263; French 683,075
Glycerol	
as a solvent for furan resins	2,345,611
Glycerol, reaction with	
furfural + fatty oil + acid	2,005,499
furfural + phthalic anhydride	1,678,105
furfural + lactide	2,174,491
furfural + glue + filler	1,468,331
linseed oil + β-(2-furyl)acrylic acid	2,382,297
Glyptal resins	
furans used with	1,678,105
furfural-phenol resin used with	1,715,688
Greases, high temperature, furfural used in	2,516,137
Halides, organic, reaction with	
furfural	2,339,059; 2,342,456
furfuryl alcohol	2,214,769
furfuryl alcohol (polymerization of)	2,399,055
Hexamethylenetetramine, used in	
furfural + filler + phenolic resin	Russian 47,078
Hexamethylenetetramine, used in	
furfural + phenol	2,414,416
furfural + phenol + filler	British 208,193
furfural-phenol-formaldehyde	1,771,508
furfural-phenol resins	1,398,146; 1,705,493–5; 1,705,496; 1,726,650; 1,737,121; 1,917,248
furfural-urea	1,827,824; 1,951,526
oil modified resin compositions	2,413,412
Hydrogenated furfuryl alcohol polymers	2,564,835

Subject	*Patents*
Impregnating solutions	
2,5-bis(hydroxymethyl)furan and α-furylglycolic acid used in	2,370,572
furfural and reaction product of phenol and furfural	1,508,261; 1,591,534; 2,325,302
furfural-furfuryl alcohol resin	2,333,151; Can. 387,514
furfural-phenol resin	1,597,538; 2,563,897
furfural + phenolic resin	1,528,006; 1,693,939 French 664,869
furfural-thiourea resins	2,568,111
furfural resin + dimethylolurea	1,536,881
furfural resin + vegetable oil	1,841,138
Inhibitor in polymerization	
furans, complex used as	2,537,015
Ion exchange resin (see Base-exchange resin)	
Ketones, reaction with	
furfural	1,441,598; 1,482,929; 1,902,256; 2,146,258
Leather, artificial	
phenol, furfural resin used in	2,302,557
Lignins, reaction with	
furfural	1,750,903; 1,899,526; 2,161,748; 2,161,749; 2,314,181; 2,310,010
furfural and an aromatic sulfamide	2,365,599
furfural + compound forming resin with furfural	2,228,567; 2,292,333–4; 2,312,320–1 2,312,688–9–90–93–96–97; 2,312,702–3–4–5; 2,317,736–7–8; 2,381,205; 2,562,898
furfural + furfuryl alcohol	2,421,623
furfural + melamine + acylated urea	2,294,873
furfural + melamine + protein	2,315,402
furfural + phenol	1,614,025; 2,148,893; 2,161,748; 2,168,160; 2,221,778; 2,282,518; 2,384,015
furfural + phenolate	2,221,778; 2,291,432–3 2,377,995; 2,494,545 2,538,302
furfuryl alcohol + formaldehyde	2,404,840; 2,521,532
furfuryl alcohol + aldehyde + aminotriazine	2,562,898
Lignocellulose material, reaction with	
furfural	1,697,248; 1,932,255; 2,096,743; 2,130,783; 2,513,316; 2,156,160; 2,313,953; 2,319,182
furfural + aniline	2,137,119; 1,153,316; 2,156,160; 2,247,206
furfural + compound forming a resin with furfural	2,137,119; 2,272,742; 2,292,333–4; 2,312,320–1 2,312,688–9–90–93–96–97;

Subject	*Patents*
Lignocellulose material, reaction with (*cont.*)	2,312,702–3–4–5; 2,317,736–7–8; 2,366,425
furfural + naphthol + rosin	2,366,425
furfural + nitric acid	2,310,010
furfural + phenol	1,892,409; 2,197,724; 2,336,672
furfural + urea	2,381,205; 2,442,897
furfuryl alcohol	2,291,432–3; 2,313,953; 2,325,570
furfuryl alcohol + urea	2,442,897
Linoleum	
linseed oil, glycerol + β-(2-furyl)acrylic acid	2,382,297
Linseed oil, reaction with	
glycerol + β-(2-furyl)acrylic acid	2,382,297
Luster, furans used to impart in paint	A.P.C. Serial No. 327,494
Melamine, reaction with (see also Aminotriazine)	
furfural	2,199,803; 2,218,474; 2,251,234; 2,259,980; 2,260,239; 2,262,728; 2,285,750; 2,310,004; 2,320,817; 2,322,566; 2,328,592; 2,331,446; 2,351,602; 2,492,510; 2,521,664; 2,537,111; 2,562,866; 2,563,898
furfural and formaldehyde	2,562,051
furfural and furfuryl alcohol	2,197,357
furfural and a phenol	2,328,592; 2,457,738
furfural and phenol-aldehyde resin	2,262,728
furfural and a protein	2,315,402
furfural, furfuryl alcohol and lignin	2,562,898
furfural and a thiazole	2,197,357
furfural and an urea	2,294,873; 2,328,593; 2,331,446
furfuryl alcohol	2,197,357
Methyl methacrylate, reaction with	
furfuryl alcohol	2,129,667
tetrahydrofurfuryl alcohol	2,129,666
Modifiers	
β-furylacrylic acid ester for natural or synthetic rubber	2,397,372
bis(tetrahydrofuryloxythiono) disulfide in butadiene polymerization	2,376,338
Molding apparatus	1,993,942
Molding hollow objects	1,776,366
Molding materials	
furfural + cellulose derivative	1,558,442; 1,840,596; 1,902,255–6–7
furfural+ decomposition product of dicyandiamide and primary aromatic amine	2,389,150
furfural + phenol-aldehyde resin	1,503,392; 1,693,112; 1,896,069; 1,451,783
furfural + vinyl ester-aldehyde gum	Reissue 20,430; 2,036,092
furfural + phenol + residue (digester)	2,397,323

Subject	*Patents*
furfural + phenolic resin + hexamethylenetetramine + waste wood	Russian 47,078
Molds formed from furfural or furfuryl alcohol resins	British 575,693
Naphthalene, reaction with furfuryl alcohol	2,321,493
Naphthol, reaction with furfural	1,377,519; 1,398,146; 1,705,493; 1,705,495; 1,737,121; 1,771,033; 1,941,708; 2,275,923
furfuryl alcohol	2,321,493
β-Naphthol, reaction with furfural and resin	2,366,425
Naphthylamine, reaction with furfural	1,902,255
α-Naphthylamine, reaction with furfural	1,441,598; 1,515,642; 1,587,273; 1,696,490; 2,275,923
β-Naphthylamine, reaction with furfural	1,441,598; 1,587,273; 1,587,274; 1,696,490; 2,146,257
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Oil, drying, used with furfural	2,058,597; 2,565,685
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carbon disulfide	2,345,611
cellulose derivative	Can. 329,708
chlorine	2,399,735
diazinal carboxy alkyl sulfide	2,393,753
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